PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07C 47/115, 255/31, 233/47
C07C 227/12, C07K 5/06
C07C 1/24, 29/78, 405/00
C07D 233/74

A2

(11) International Publication Number: **WO 91/02711**

(43) International Publication Date: 7 March 1991 (07.03.91)

(21) International Application Number: PCT/US90/04722

(22) International Filing Date: 20 August 1990 (20.08.90)

(30) Priority data:
396,586 21 August 1989 (21.08.89) US
64/2131116 21 August 1989 (21.08.89) JP

(71) Applicants: THE COCA-COLA COMPANY [US/US]; P.O. Drawer 1734, Atlanta, GA 30301 (US). TAKASAGO INTERNATIONAL CORPORATION [JP/JP]; 19-22, 3-chome, Takanawa, Minato-ku, Tokyo (JP).

(72) Inventors: YUASA, Yoshifumi ; 2-6-6-305 Toyogaoka, Tama-shi, Tokyo (JP). TACHIKAWA, Ako ; 2-12-23 Shinmachi, Tsujido, Fujisawa-shi, Kanagawa-ken (JP). OKETA, Yoshiki ; 204, 3-1, Kurobegaoka, Hiratsuka-shi, Kanagawa-ken (JP). WATANABE, Toru ; 253-18 Shimohongo, Toyoda-machi, Iwata-gun, Shizuoka-ken (JP). NAGAKURA, Akira ; 3-6-4 Hon-cho, Kawaguchi-shi, Saitama-ken (JP). SWEENY, Jamges, G. ; 2484 Oldfield Road, N.W., Atlanta, GA 30300 (US). KING, Georga, A., III ; 858 Kings Court, N.E., Atlanta, GA 30306 (US).

(74) Agents: LEE, William, C., III; The Coca-Cola Company, NAT 2038, P.O. Drawer 1734, Atlanta, GA 30301 (US) et al.

(81) Designated States: AT (European patent), AU, BE (European patent), BR, CA, CH (European patent), DE (European patent)*, DK (European patent), ES (European patent), FR (European patent), GB (European patent), IT (European patent), LU (European patent), NL (European patent), SE (European patent).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: 7,7-DIMETHYLNORBORNANE DERIVATIVES

(57) Abstract

The present invention discloses 7,7-dimethylnorbor- nane derivatives useful as intermediates for the production of various synthetic perfumes and high intensity sweeteners. 2R-exo-7,7-Dimethylnorbornyl acetaldehyde, 3-(2R-exo-7,7-dimethylnorbornyl)-2-amino- propionitrile,3-(2R-exo-7,7-dimethylnorbornyl)alanine hydantoin and N-acyl-3-(2R-exo-7,7-dimethylnorbornyl) alanines are disclosed. The present invention describes a process for making 7,7-dimethylnorbornane derivatives, 3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine lower alkyl esters and alpha-L-aspartyl-3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine lower alkyl esters. A process for making alpha-fenchene, a process for making alpha-fenchyl alcohol and a process for making an optically active 3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine or its lower alkyl ester are also disclosed. Dehydration and rearrangement catalysts are also disclosed.

* See back of page

DESIGNATIONS OF "DE"

Until further notice, any designation of "DE" in any international application whose international filing date is prior to October 3, 1990, shall have effect in the territory of the Federal Republic of Germany with the exception of the territory of the former German Democratic Republic.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

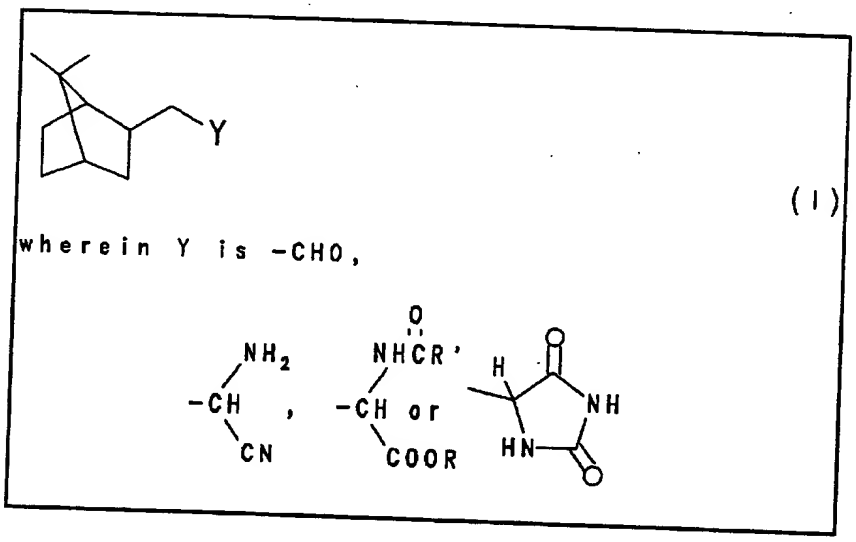
AT	Austria	ES	Spain	MC	Monaco
AU	Australia	FI	Finland	MG	Madagascar
BB	Barbados	FR	France	ML	Mali
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Fasso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GR	Greece	NL	Netherlands
BJ	Benin	HU	Hungary	NO	Norway
BR	Brazil	IT	Italy	PL	Poland
CA	Canada	JP	Japan	RO	Romania
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CM	Cameroon	LI	Liechtenstein	SU	Soviet Union
DE	Germany	LK	Sri Lanka	TD	Chad
DK	Denmark	LU	Luxembourg	TG	Togo
				US	United States of America

7,7-DIMETHYLNORBORNANE DERIVATIVES

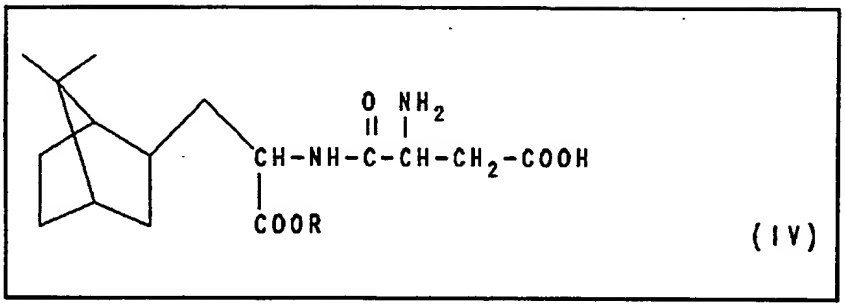
BACKGROUND AND SUMMARY

This invention relates to novel norbornane derivatives and processes for their preparation and conversion of such derivatives to high intensity artificial sweeteners. In addition, this invention also relates to novel catalysts for the preparation of fenchyl alcohol and alpha-fenchene.

The novel norbornane derivatives of this invention are more specifically represented by formula (I) as follows:



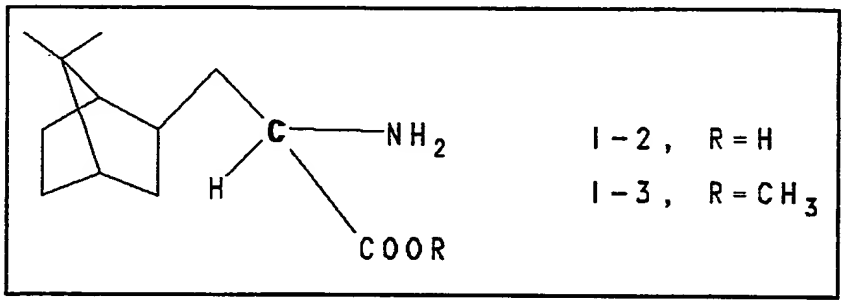
wherein R is hydrogen or a lower alkyl group of one to three carbons and wherein R' is hydrogen or a lower alkyl group of one to three carbons. The compounds of formula (I) are very useful as intermediates for the production of high intensity sweeteners, particularly L-aspartyl-3-(7,7-dimethylnorbornyl)-L-alanine derivatives of the f ll wing formula:



(IV)

wherein R is a lower alkyl group of one to three carbons. Such high intensity sweeteners are described in U.S. Patent No. 4,788,069.

In U.S. Patent No. 4,788,069 the preparation of sweetener (IV) involves the synthesis of the amino acid I-2 and the amino ester I-3, the later being prepared from the former via esterification with methanolic hydrochloric acid.

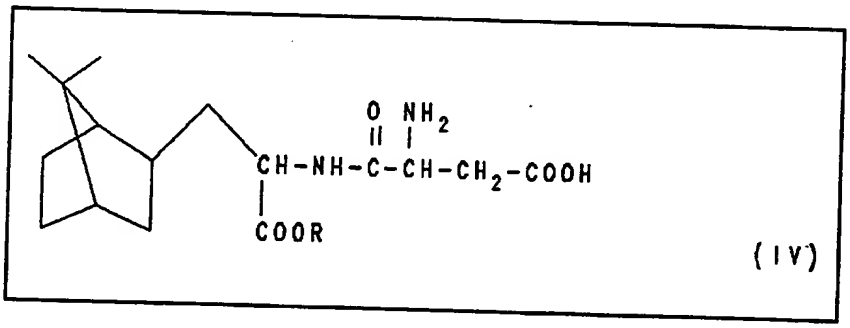


Two methods are disclosed for the preparation of I-2 and related bicyclic amino acids. In the first, alpha-fenchene is converted to the corresponding 7,7-dimethylnorbornyl-2-methanol using diborane and hydrogen peroxide. This intermediate is then converted to the tosylate and condensed with sodium dimethylmalonate to give a norbornyl malonic acid diester. To finally arrive at amino acid I-2, three

additional steps, bromination, hydrolysis and amination, are required. The overall process known in the art is very expensive and gives only low yields of the I-2. In the second method, alpha-fenchene is treated with 9-borabicyclo[3.3.1]nonane and the resulting hydroboration product condensed with methyl-N-(diphenylmethylene)-2-acetoxyglycinate to give an adduct which can be hydrolyzed to I-3 with dilute acid. This method, although much simpler than the first, involves the use of very expensive reagents and would not be economical on an industrial scale.

The present invention overcomes the disadvantages of the prior art by converting alpha-fenchene directly to the novel aldehyde I-1 either via reductive carbonylation or via the Vilsmeier reaction and catalytic hydrogenation. See Reaction Schemes A and B. The novel norbornyl aldehyde I-1 can be readily converted to amino acid I-2 via I-4 (the Strecker reaction) or via I-5 (the hydantoin procedure). In both cases yields are high and reagent costs low.

The present invention provides a process for making 3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine lower alkyl esters represented by the following formula:



(IV)

wherein R represents a lower alkyl group of 1 to 3 carbon atoms comprising the steps of: (a) rearranging (-)-trans-2-

pinanol to form (+)-alpha-fenchyl alcohol; (b) dehydrating (+)-alpha-fenchyl alcohol to form (+)-alpha-fenchene; (c) converting the (+)-alpha-fenchene to 2R-exo-7,7-dimethylnorbornyl acetaldehyde; (d) converting 2R-exo-7,7-dimethylnorbornyl acetaldehyde to 3-(2R-exo-7,7-dimethylnorbornyl)-D,L-alanine (e) resolving 3-(2R-exo-7,7-dimethylnorbornyl)-D,L- alanine to produce 3-(2R-exo-7,7-dimethylnorbornyl)-L- alanine; and (f) esterifying 3-(2R-exo-7,7-dimethylnor- bornyl)-L-alanineto form 3-(2R-exo-7,7-dimethylnorbor- nyl)-L-alanine lower alkyl ester. In the above process step (d) may comprise converting the acetaldehyde to an aminonitrile and hydrolyzing the nitrile to form 3-(2R-exo-7,7-dimethylnorbornyl)-D,L-alanine. Alternatively, in the above process step (d) may comprise converting the acetaldehyde to a hydantoin and hydrolyzing the hydantoin to form 3-(2R-exo-7,7-dimethyl- norbornyl)-D,L-alanine. In the above process the step of resolving may occur after the step of esterifying.

In step (a) (+)-alpha-fenchyl alcohol is produced by reacting (-)-trans-2-pinanol with a catalyst selected from the group of aluminum phosphate, niobium oxide and nickel sulfate.

General methods of producing alpha-fenchyl alcohol include, for example, (1) the Wagner-Meerwein type rearrangement reaction of alpha- or beta-pinene with mineral acids or organic acids [G. G. Henderson et al., J. Chem. Soc., 125, 107-13 (1924)], (2) the reduction of fenchone with various reducing agents, for example metallic sodium and alcohol [W. Huckel et al., Chem. Ber. 90, 2025 (1957); P. Teisseire et al., Recherches, 19, 232 (1974)] and (3) the rearrangement of trans-2-pinanol with perchloric acid or acetic anhydride [H. Indyk et al., J. Chem. Soc. Perkin II,

3113 (1974), W. D. Burrows et al., J. Am. Chem. Soc. 81, 245 (1959)].

In the Wagner-Meerwein type reaction in method (1), the selectivity of alpha-fenchyl alcohol or alpha-fenchyl alcohol derivative is 10% or less, and it is difficult for this method to give alpha-fenchyl alcohol at a high selectivity. In method (2), the production of fenchone itself is complex [G. Buchbauer et al., Liebigs. Ann. Chem., 2093 (1981)]. Method (3) is not economically feasible because it requires acetic anhydride or a large amount of solvent and the product is obtained as alpha- fenchyl acetate.

The present invention overcomes the problems of the prior art and provides an economical industrial method of producing alpha-fenchyl alcohol from trans-2-pinanol as a starting material.

In step (b) above, (+)-alpha-fenchyl alcohol is converted to (+)-alpha-fenchene by heating in the presence of a specially prepared aluminum oxide catalyst disclosed herein.

One prior process for producing alpha-fenchene comprises solvolyzing fenchyl tosylate with acetic acid in the presence of an excess of sodium acetate thereby giving alpha fenchene in a selectivity of 90% [W. Hueckel et al., Liebigs Ann. Chem. 664, 31 (1963)]. However, this process is economically and industrially disadvantageous because tosylation of fenchyl alchol requires a large amount of pyridine and a long period of reaction time and the solvolysis requires a large amount of acetic acid. As a method of dehydrating and rearranging fenchyl alcohol to alpha-fenchene, the use of potassium sulfate [W. Hueckel et al., Liebigs Ann. Chem., 687, 40 (1965)], the use of aluminum phosphate [D. Tishchenko et al., Zhur. Obshchei Khim., 22, 1824-29 (1952)], and the use of kaolin or zinc chloride [E. Pulkkinen, Suomen Kemistilehti,

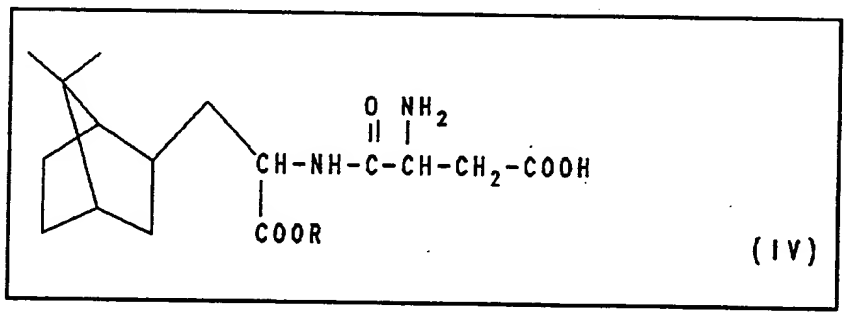
30A, 239 (1957)] are known. In all of these methods, the selectivity and yields of alpha-fenchene are about 20 to 30%, and are not industrially satisfactory.

The present invention overcomes the above disadvantages of the prior art and provides a commercial process utilizing a solid acid catalyst and heat to convert fenchyl alcohol to alpha-fenchene with high selectivity and high yield.

The present invention also discloses a process for purifying (+)-alpha-fenchyl alcohol, which comprises crystallizing alpha-fenchyl alcohol in a hydrocarbon solvent at low temperatures.

In steps (c) through (f) described above the intermediate (+)-alpha-fenchene is converted to amino acid ester I-3 via the novel intermediates I-1, I-4, and I-5 using procedures described in the literature. See Reaction Schemes A and B and the specification below.

The present invention also provides a process for producing alpha-L-aspartyl-3-(2R-exo-7,7-dimethylnorbor- nyl)-L-alanine lower alkyl ester represented by the following formula:



(IV)

wherein R is a lower alkyl group of one to three carbon atoms comprising the steps of: (a) coupling 3-(2R-exo-7,7-

dimethylnorbornyl)-L-alanine lower alkyl ester with an N-protected aspartic acid anhydride to produce an N-protected-(alpha/beta)-L-asparty1-3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine lower alkylester; (b) deprotecting the N-protected-(alpha/beta)-L-asparty1-3-(2R-exo-7,7-dimethylnorbornyl)L-alaninelower alkyl ester to produce a mixture of alpha and beta-L-asparty1-3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine lower alkyl esters; and (c) separating the alpha-L-asparty1-3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine lower alkyl ester from the mixture. The step of deprotecting may occur after the step of separating. An N-protected aspartic acid having a beta-ester protecting group may be utilized for the N-protected aspartic acid anhydride.

The present invention also discloses a process for producing an optically active 3-(2R-exo-7,7-dimethylnor-bornyl)-L-alanine or its lower alkyl ester, which comprises treating an N-acyl-3-(2R-exo-7,7-dimethylnor- bornyl)-D,L-alanine or its lower alkyl ester with an acylase in an aqueous medium, and recovering the resulting 3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine or its lower alkyl ester.

In the present invention, the term "lower" used to qualify a group or a compound includes methyl, ethyl, n-propyl, and isopropyl groups.

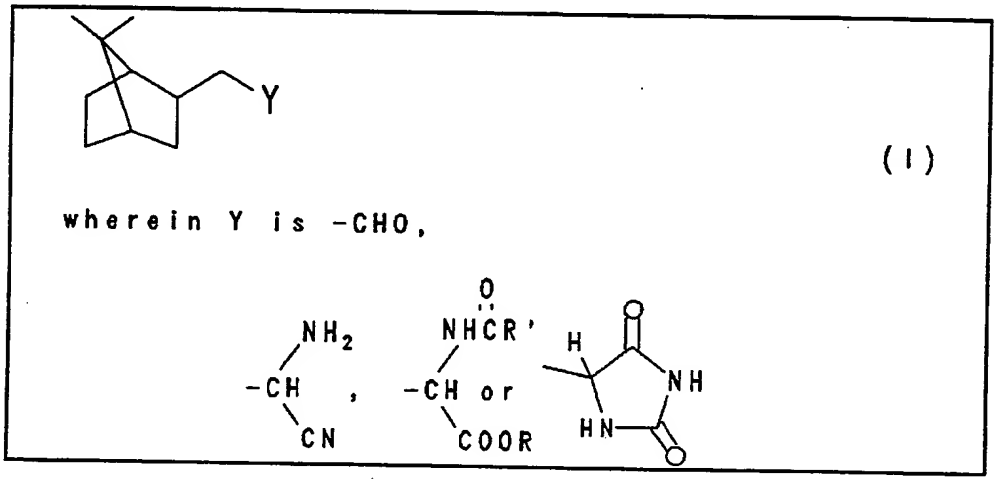
An advantage of the present invention is to provide the novel 7,7-dimethylnorbornane derivatives of formula (I) which are useful as synthesis intermediates for the preparation of L-asparty1-3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine derivatives of formula (IV), particularly the compound of formula (IV-1, R=CH_3), which are useful as sweeteners having high sweetening power.

Another advantage of the present invention is to provide a process for producing the L-asparty1-3-(7,7-

dimethylnorbornyl)-L-alanine derivatives of formula (IV) useful as sweeteners from the novel 7,7-dimethylnorbor- nane derivatives of formula (I).

Another advantage of the present invention is to provide novel catalysts useful in the preparation of fenchyl alcohol and alpha-fenchene.

In summary the present invention discloses compounds represented by the following formula:



wherein R is hydrogen or a lower alkyl group of one to three carbons and wherein R' is hydrogen or a lower alkyl group of one to three carbons. The present invention discloses 2R-exo-7,7-dimethylnorbornyl acetaldehyde, 3-(2R-exo-7,7-dimethylnorbornyl)-2-aminopropionitrile and 3-(2R-exo-7,7-dimethylnorbornyl)alanine hydantoin. A compound comprising N-acyl-3-(2R-exo-7,7-dimethylnorbor- nyl)-D,L-alanine, wherein acyl is acetyl, propionyl, butyryl or chloroacetyl is disclosed in the present invention. Specifically, N-acetyl-

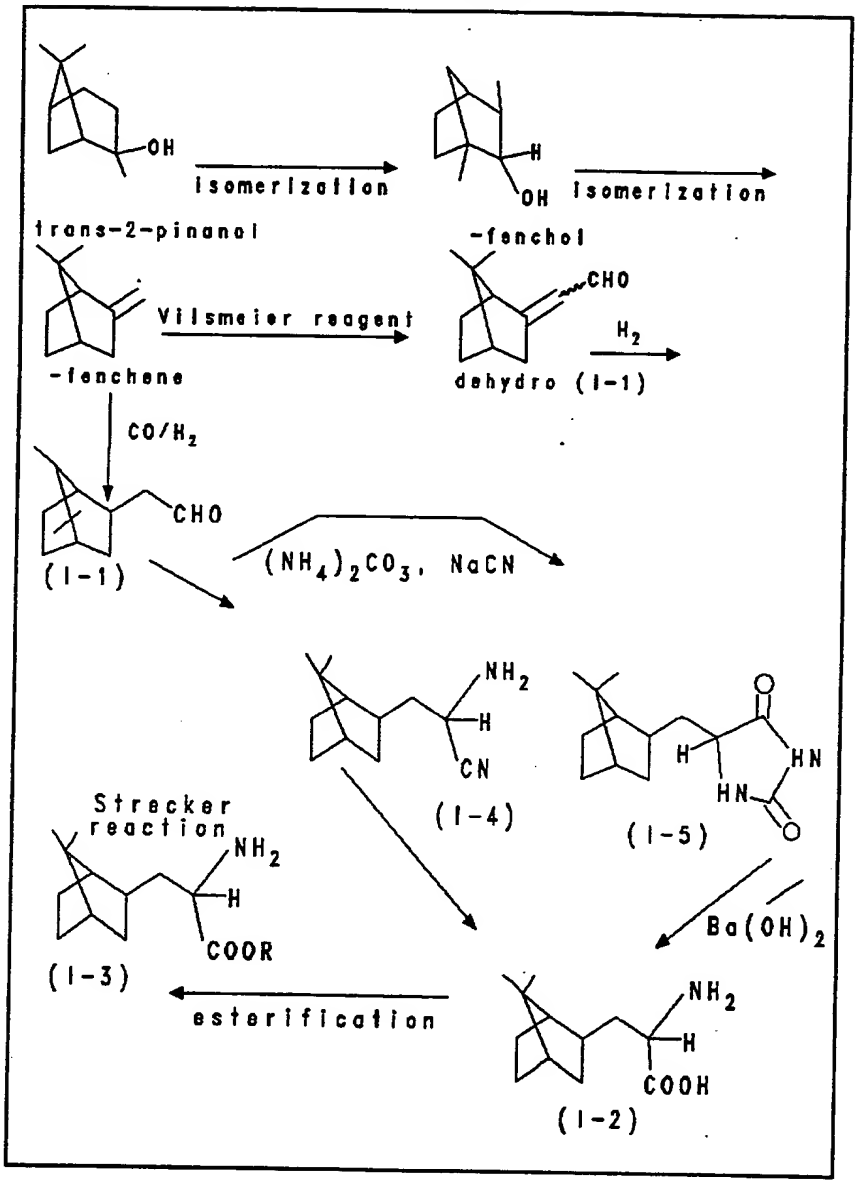
3-(2R-exo-7,7-dimethyl-norbornyl)-D,L-alanine and N-chloroacetyl-3-(2R-exo-7,7- dimethylnorbornyl)-D,L-alanine are disclosed.

A fenchyl alcohol dehydration catalyst selected from the group consisting of calcined aluminum oxide is disclosed; specifically, the dehydration catalyst comprising calcined aluminum oxide having Hammett acidity function of $-5.6<H^{\circ}\leq-3.0$ is described. Finally, there is also disclosed a catalyst for producing alpha-fenchyl alcohol from trans-2-pinanol, selected from the group aluminum phosphate, niobium oxide and nickel sulfate.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The compounds of formula (I) in accordance with this invention [the compounds of formulae (I-1), (I-2) and (I-3) in the following reaction scheme] may be produced by a synthetic route summarized in the following reaction Scheme A.

Reaction Scheme A



In the above Reaction Scheme A, alpha-fenchyl alcohol is prepared in a high conversion and at a high selectivity by heating trans-2-pinanol to a temperature of 60 to 150°C in the presence of one or more catalysts selected from aluminum phosphate, niobium oxide and nickel sulfate.

This method will be described below in detail. Trans-2-pinanol used as a starting material in this method can usually be obtained by subjecting nopinone (obtained by oxidation of beta-pinene with ozone or potassium permanganate) to Grignard reaction with a methyl magnesium halide [W. Huckel et al., Liebigs, Ann. Chem., 625, 12, (1959)], or by catalytically reducing alpha- or beta-pinene to form pinane, oxidizing it with oxygen and reducing it further [S. G. Traynor et al., J. Org. Chem., 45, 900 (1980).

Aluminum phosphate used as the catalyst in this invention can be obtained by hydrolyzing hydrous aluminum nitrate, hydrous aluminum sulfate, hydrous aluminum chloride or sodium aluminate with an aqueous solution of a nonmetallic alkali, i.e. ammonia or urea, adding an equivalent weight of ortho-phosphoric acid to the resulting aluminum hydroxide to permit precipitation, and calcining the resulting hydrous aluminum phosphate at a temperature of 300 to 800°C, preferably 300°C, for about 3 hours.

Niobium oxide used as the catalyst in the method of this invention may contain water. Niobium oxide and its hydrate (so-called niobic acid) may generally be produced by precipitation from a solution of a niobium compound such as niobium chloride or niobium oxalate by the action of an alkali. Usually, the resulting precipitate contains a considerable amount of water, but it can be dehydrated almost completely by heating to more than 200°C. Niobic acid

obtained by precipitation from solution can be used as such or after calcination at 500°C or below, as niobium oxide.

Nickel sulfate as another catalyst can be prepared by calcination of a commercially available nickel sulfate hydrate.

The treatment of trans-2-pinanol in the presence of the catalyst may be carried out at a temperature of 60 to 150°C, preferably 65 to 75°C.

The suitable amount of the catalyst used is about 1 to 10% by weight based on the trans-2-pinanol. The reaction in this invention is usually performed without solvent. In view of the separation of the desired compound from the reaction products, the conversion of trans-2-pinanol is preferably at least 90%.

After the reaction, the reaction mixture is filtered to remove the catalyst, and the residue distilled in a customary manner. Alternatively, the reaction mixture may be directly distilled without separation of the catalyst.

The starting trans-2-pinanol includes a (+)-form and a (-)-form, and its optical purity can be determined by its specific rotation. The present inventors condensed trans-2-pinanol with N-carbobenzyloxy-(D)- or (L)-alanoyl chloride in the presence of pyridine, removed the N-protecting group from the reaction product, and measured its optical purity by gas chromatography (the gas chromatographic column is, for example, a PEG-HT capillary, 0.25 mm. in diameter, 25 m. in length; made by Gasukuro Kogyo Co., Ltd.,). Alpha-fenchyl alcohol obtained by the method of this invention also includes a (+)-form and a (-)-form. The use of either the (+)-form or (-)-form of trans-2-pinanol can give either one of these forms. For example, if the method of this invention is carried out by using (-)-trans-2-pinanol obtained by the

method of the above-cited Liebigs Ann. Chem., 625, 12, (1959) as the starting material, (+)-alpha-fenchyl alcohol is obtained without racemization.

The method of this invention can economically give alpha-fenchyl alcohol useful as a material for a perfume or as a sweetener intermediate as described below.

In the above Reaction Scheme A, fenchyl alcohol is heated in the presence of a solid acid catalyst to perform a dehydration and isomerization reaction simultaneously to selectively produce alpha-fenchene.

It has now been found in accordance with this invention that aluminum oxide is especially suitable as the solid acid catalyst used in this reaction. Especially suitable is aluminum oxide prepared by hydrolyzing hydrous aluminum nitrate, hydrous aluminum sulfate, hydrous aluminum chloride or sodium aluminate with an aqueous solution of a non-metallic alkali such as ammonia or urea and calcining the resulting aluminum hydroxide. More specifically, this aluminum oxide is obtained by dispersing a 10% by weight aqueous solution of aluminum nitrate hydrate in 28% aqueous ammonia at room temperature to hydrolyze it, separating and recovering the resulting aluminum hydroxide precipitate by filtration in a customary manner, and calcining the resulting aluminum hydroxide at a temperature range of from about 400 to 600°C, preferably about 500°C, for about 3 hours. The acid strength of the aluminum oxide prepared under these conditions, expressed by the Hammett acidity function, is $-5.6<Ho\leq-3.0$. It is a solid acid of a medium acidity.

For the conversion to fenchene the solid acid can generally be used in an amount of 0.1 to 10%, preferably 1 to 5%, based on the weight of the starting fenchyl alcohol.

The reaction temperature is usually in a range from about 150 to 250°C, particularly 195 to 200°C. If the reaction temperature is too low, the rate of the reaction becomes slow. The reaction time varies with the fenchyl alcohol used, but usually a period of time ranging from about 1 to 24 hours suffices.

The presence of water in the reaction system in the above reaction is undesirable, and it is preferred to carry out the reaction in a reactor equipped with a water removing device such as the Dean-Stark device. Usually, the reaction can be carried out without using a solvent.

After the reaction, the reaction mixture is distilled with or without prior separation of the catalyst, and as required, rectified in a rectification column.

The starting fenchyl alcohol may be either alpha-fenchyl alcohol or beta-fenchyl alcohol. Alphafenchyl alcohol can be obtained commercially or prepared from trans-2-pinanol as described above. Beta-fenchyl alcohol can be obtained in a high purity by catalytically reducing fenchone, converting the resulting mixture of alpha- and beta-fenchyl alcohols into their crystalline p-nitrobenzoates, recrystallizing repeatedly, and hydrolyzing the purified product. Alternatively, a mixture of alpha-fenchyl alcohol and beta-fenchyl alcohol may be obtained by epimerizing alpha-fenchyl alcohol under hydrogen pressure in the presence of a copper-chromium catalyst.

In the production of L-aspartyl-3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine methyl ester of formula (IV-1, R=CH3) in particular, the use of (+)-alpha-fenchyl alcohol as the starting material is preferred. The (+)-alpha-fenchyl alcohol may be isolated and purified in a high optical purity of, for example, about 94% e.e. by crystallizing commercial

alpha-fenchyl alcohol in a hydrocarbon type organic solvent at low temperatures.

The commercially available alpha-fenchyl alcohol is generally a mixture of the (+)-alpha-isomer and the (-)-alpha-isomer in a weight ratio of from 80:20 to 70:30. Crystallization of the commercial alpha-fenchyl alcohol in an aliphatic hydrocarbon solvent such as n-pentane, n-hexane, isohexane, n-heptane, n-octane and isooctane (preferably n-heptane or n-octane) gives the (+)-alpha-isomer of high purity, for example an optical purity of 94 % e.e. or more.

The crystallization treatment can be carried out by dissolving the alpha-fenchyl alcohol in the solvent at room temperature or at a slightly elevated temperature and cooling the solution to a temperature of about -10 to -60°C, preferably -35 to -60°C.

A product having a sufficient optical purity may be obtained by one crystallization, but by repeating the crystallization two or three times, a product of a very high optical purity can be obtained.

The optical purity of the purified (+)-alpha- fenchyl alcohol can be determined by its specific rotation. The present inventors measured the optical purity of the alpha-fenchyl alcohols by gas chromatography of their L-alanine or D-alanine esters (the column may be, for example, PEG-HT capillary, 0.25 mm in diameter and 25 m in length, made by Gasukuro Kogyo K. K.). The sample was prepared by condensing alpha-fenchyl alcohol with N-carbobenzyloxy-(D) or (L)-alanine using a dehydrating agent such as dicyclohexylcarbodiimide (DCC) or 1-ethyl-3- (3-dimethylamino- propyl)carbodiimide hydrochloride in the presence of N,N-dimethylaminopyridine, or by condensing alpha- fenchyl alcohol with N-butoxycarbonyl-(D) or (L)-alanine using the above dehydrating agent.

The amino protecting groups are then removed by hydrogenation (the N-carbobenzyloxy group) or acid treatment (the N-t-butoxycarbonyl group) prior to G.C. analysis.

In the above dehydration-isomerization reaction of fenchyl alcohol to alpha-fenchene, the rate of the reaction of beta-fenchyl alcohol is faster than that of its alpha-epimer. The reaction with beta-fenchyl alcohol generally comes to completion within 3 hours, and alpha-fenchene forms with a selectivity of about 80%. On the other hand, when alpha-fenchyl alcohol is used as the starting material, the selectivity for alpha-fenchene after 16 hours is about 59%. When a mixture of alpha- and beta-fenchyl alcohols (alpha/beta = 6/4) is used, the selectivity for alpha-fenchene is increased to 65%.

The alpha-fenchene so obtained is subjected to the Vilsmeier reaction to form 7,7-dimethyl-2-formyl-methylenenorbornane. Stereoselective reduction of this product yields 2R-exo-7,7-dimethylnorbornyl acetaldehyde (I-1).

The Vilsmeier reaction of alpha-fenchene can be carried out by a known method described, for example, in C. Jutz et al., Chem. Ber. 100, 1536 (1967). For example, alpha-fenchene is added to the Vilsmeier reagent prepared at room temperature from phosgene or thionyl chloride and an N,N-disubstituted formamide such as N-methylformanilide; preferably from phosphorus oxychloride and more than one equivalent of N,N-dimethylformamide. The mixture is reacted at a temperature of 50 to 90°C to give dehydro-(I-1) as an E-/Z- mixture.

The resulting 7,7-dimethyl-2-formylmethylenenorbornane [dehydro-(I-1)] is reduced to give 2R-exo-7,7-dimethyl-norbornyl acetaldehyde of formula (I-1). Reduction of

dehydro-(I-1) may be carried out by a catalytic hydrogenation method using hydrogen in the presence of a noble metal catalyst such as palladium on carbon. As a result, the compound of formula (I-1) can be obtained with an exo-selectivity of as high as or greater than about 95%.

As an alternative, alpha-fenchene may be directly converted to 7,7-dimethylnorbornyl-2-acetaldehyde of formula (I-1) by oxo reaction using various rhodium complex catalysts. According to this method, the selectivity of the exo-form of formula (I-1) is somewhat inferior to that in the method which goes through dehydro-(I-1).

The oxo reaction of alpha-fenchene may be carried out in the same way as an ordinary oxo reaction described, for example, in W. Himmele et al., Tetrahedron Letters, 907, 1976 and J. Hagen and K. Bruns, U.S. Patent No. 4,334,100. For example, alpha-fenchene is hydroformylated with a gaseous mixture of carbon monoxide and hydrogen at a temperature of about 30 to about 150°C under a gas pressure of about 25 to about 150 kg/cm2 in the presence of a rhodium complex catalyst, for example a rhodium carbonyl complex such as Rh6(CO)16, RhCl(CO)(pph3)2 (pph3 stands for triphenylphosphine), RhH(CO)(pph3)3, [Rh(COD)X]2 (COD stands for cyclooctadienyl and X is halogen, acetate) or Rh(COD)(acac) (acac stands for acetyl acetonate).

The resulting 2R-exo-7,7-dimethylnorbornyl acetaldehyde of formula (I-1) is then reacted with ammonia or ammonium chloride and hydrogen cyanide or an alkali cyanide in accordance with Strecker'samino acid synthesis method [see, for example, J.P. Greenstein & M. Winitz, "Chemistry of the Amino Acids," Vol. I, pg. 698-700 (1961); R. Gardry, Can. J. Res., 24B, 301 (1946)]. The resulting 3-(2R-exo-7,7-dimethylnorbornyl) -2-amino propionitrile (I-4) is hydrolyzed

under acidic conditions created by a mineral acid such as hydrochloric acid, hydrobromic acid or hydriodic acid to give 3-(2R-exo-7,7-dimethylnorbornyl)-D,L-alanine of formula (I-2).

The Strecker reaction can be conducted in alcoholic or mixed alcoholic-aqueous solution using ammonia gas or ammonium hydroxide solution. The cyanide can be supplied as the Li, Na or K salt, the more soluble Li and Na salts being preferred. Reaction temperatures of 0 to 30°C may be employed, the time being adjusted accordingly. After removal of the solvent by evaporation the residue is treated with a strong base (such as NaOH, KOH or Na2CO3) and the aminonitrile extracted with ether, toluene, or any suitable organic solvent which does not react with the amino function.

Hydrolysis of the resulting 3-(2R-exo-7,7-dimethyl-norbornyl)-2-amino propionitrile is best achieved by refluxing in approximately 10 N HCl solution for 18 hours. Lower acid concentrations may be used, but longer reaction times are required. Shorter reaction times may be achieved by heating at elevated temperatures in an autoclave. Other acids may also be employed such as hydrobromic or sulfuric. Hydrochloric is particularly useful in that the product can be obtained as the hydrochloride by direct crystallization from the cooled, concentrated reaction mixture.

An alternative method for producing the amino acid of formula (I-2) involves preparation of an intermediate hydantoin. In this procedure, the 2R-exo-7,7-dimethyl-norbornyl acetaldehyde of formula (I-1) is reacted with an alkali metal cyanide and ammonium carbonate. [Bücherer-Berg reaction - see H. R. Henze and R. J. Speer, J. Am. Chem. Soc., 64, 522-3 (1942) and E. Wade, Chem. Rev., 46, 441-4, (1950)].

The resulting hydantoin (I-5) is then hydrolyzed with a strong aqueous base [NaOH, Ba(OH)2] to afford the amino acid (I-2).

In a typical procedure, one mole of the aldehyde is heated at 50-70°C for 8-24 hours with 2-5 moles of (NH4)2CO3 and 1.1 moles of NaCN in an aqueous ethanolic solution. The mixture is cooled, concentrated and acidified to pH ~~ 5 to precipitate the product (I-5) as a white solid.

Hydrolysis of (I-5) to the amino acid (I-2) is then achieved by refluxing in 1.5 M Ba(OH)2 solution for 72 hours.

The 3-(2R-exo-7,7-dimethylnorbornyl)alanine of formula (I-2) produced as above is generally obtained as a mixture of the D-form and L-form. The mixture must, therefore, be optically resolved and the L-form suitable as a sweetener intermediate recovered.

Optical resolution may be carried out before or after the compound of formula (I-2) is esterified.

Esterification of the compound of formula (I-2) can be carried out by reacting it with a lower alkanol having from one to three carbon atoms.

For example, esterification of (I-2) with methanol is readily achieved by heating a solution of the amino acid in methanolic hydrogen chloride solution for 18 hours at reflux. Evaporation of the solvent affords the amino ester hydrochloride. The free base (I-3, R=CH3) is then obtained by neutralizing an aqueous solution of the hydrochloride with a suitable base (KOH, NaOH, Na2CO3) and extracting the product into ether, toluene or other organic solvents which are not base-sensitive. Evaporation of the extract gives the pure amino ester (I-3, R = CH3).

Optical resolution of 3-(2R-exo-7,7-dimethylnorbor- nyl)-D,L-alanine (I-2) or its lower alkyl ester (I-3) may be

carried out by known methods such as using D-tartaric acid or an enzyme.

(1) Optical resolution with D-tartaric acid is practiced on the 3-(2R-exo-7,7-dimethylnorbornyl)-D,L-alanine lower alkyl ester by heating a one to one mixture of D-tartaric acid and the amino ester in methanol until the D-tartaric acid goes into solution. The solution is then cooled to induce crystallization. Two further recrystallizations gives material of >95% ee.

If possible, the alcohol used for the crystallizations should be the same as that represented by the R group of (I-3) so that trans-esterification is avoided.

(2) Optical resolution by the enzyme method.

The compound of formula (I-2 or I-3) is N-acylated (for example, N-acetylated or N-chloroacetylated) in a known manner and acylase is caused to act on the acylated compound in an aqueous medium. As a result, the L-form of N-acyl-3-(2R-exo-7,7-dimethylnorbornyl)-D,L-alanine or its ester is selectively deacetylated to give 3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine or its ester.

The acylase that can be used in the enzyme reaction may be of any type which has the ability to hydrolyze the L-form of an N-acylamino acid selectively [see for example I. Chibata, et al., in K. Mosbach, ed., Methods in Enzymology, Vol. 44, 746-59, (1976)]. It may be originated from an animal source, a plant source or a microorganism source. Since the acylase reaction is generally carried out in weak alkalinity, the acylase preferably has an optimal pH in the range of from about 6 to 9. The acylase may be obtained by culturing a microorganism, for example a mold of the genus Aspergillus or Penicillium, a bacterium of the genus Pseudomonas, or an actinomyces of the genus Streptomyces, and recovering the

acylase from the culture. For example, Acylase I (Sigma Chemical Company) and Acylase "Amano" (Amano Pharmaceutical Co., Ltd.; derived from Aspergillus welleus) are commercially available.

Deacylation of the N-acyl-3-(2R-exo-7,7-dimethylnorbornyl)-D,L-alanine (I-6) or its ester using such an acylase may be carried out in the same way as in an ordinary enzyme reaction. For example, the N-acyl compound is dissolved or dispersed in an aqueous medium. The pH of the medium is adjusted to the optimal pH of the acylase with an alkali such as sodium hydroxide or sodium carbonate. If desired, an enzyme stabilizer such as cobalt chloride hexahydrate is added so that the cobalt ion concentration becomes 10^{-6} to 10^{-2}M. The reaction is carried out at a temperature range of from about 35 to 40°C for several hours to more than 10 hours.

After the reaction, the pH of the reaction mixture is adjusted to an acidic pH, for example about 1 to about 2, and the unreacted N-acyl-3-(2R-exo-7,7-dimethylnorbor- nyl)alanine or its ester is separated and recovered using a solvent such as ethyl acetate, methylene chloride or chloroform. In the case of the acid (I-2) the aqueous layer is adjusted to a pH range of from about 3 to 5 with aqueous ammonia. The desired 3-(2R-exo-7,7-dimethylnor- bornyl)-L-alanine precipitates as crystals. The crystals are separated and purified by a customary method, for example by treatment with activated carbon in hot water. White purified 3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine can thus be recovered. In the case of the ester (I-3, R=CH3) the aqueous layer is adjusted to pH 8-9 (instead of 3-5) and the product isolated by extraction with a solvent such as ethyl acetate, chloroform or methylene chloride. Evaporation of the solvent gives 3-(2R-

exo- 7,7-dimethylnorbornyl)-L-alanine methyl ester as a liquid.

The purified 3-(2R-exo-7,7-dimethylnorbornyl)-L- alanine or its ester has an optical purity, determined by gas chromatography using a specially worked capillary (G-800 column made by Chemical Inspection & Testing Institute) after N-trifluoroacetylation and as required esterification, of substantially 100%.

The unreacted N-acyl-3-(2R-exo-7,7-dimethyl- norbornyl)-D-alanine or its ester may be converted to 3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine or its ester by a known method, for example, by treating it with acetic anhydride to racemize it, and subjecting the racemate again to the acylase reaction.

The N-acyl derivative of (I-2) used in the above enzymatic resolution procedure can in principle also be prepared by the direct amido carbonylation of either alpha-fenchene or the 7,7-dimethylnorbornyl-2-acetalde- hyde

(I-1) using CO/H2, R-C(=O)-NH2 and a catalyst. [The amido-carbonylation reaction -- see I. Ojima, J. Mol. Catal., 37, 25-44 (1986); P. Magnus and M. Slater, Tet. Let., 28, 2829 (1987); K. Izawa, J. Syn. Org. Chem. Jp., 46, 218 (1988) and Japanese Patent No. 61/236760.

Typical conditions require the alkene (or aldehyde), a combined cobalt-rhodium catalyst, carbon monoxide, acetamide, hydrogen (500-2000 psi) and a temperature of 80-150°C for 1-10 hours.

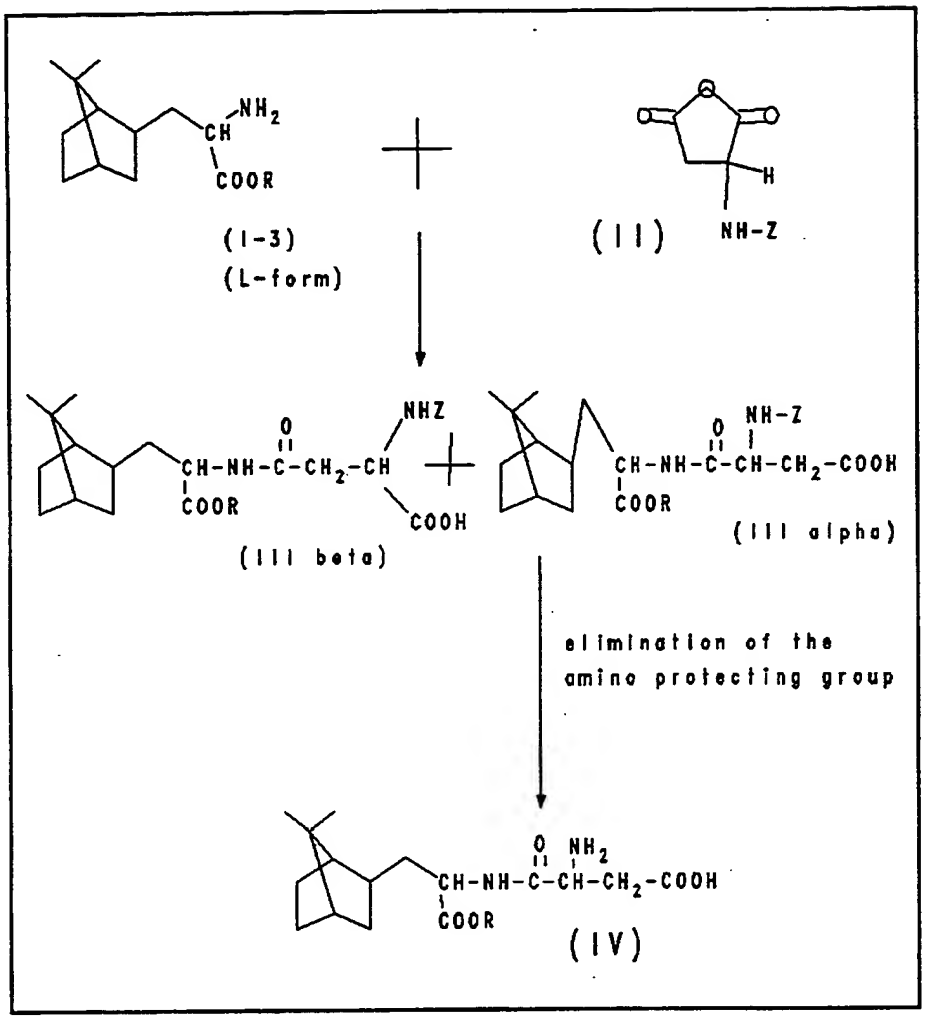
A third method of resolving the amino acid of Formula (I-2) can also be envisioned, which involves treating the hydantoin (I-5) with a microbial enzyme capable of selective hydrolysis of the hydantoin ring to afford the L-amino acid. Although most hydantoinase enzymes give the D-amino acid as

the only product, the enzyme isolated from Bacillus brevis has been found to give the desired L-isomer in the case of valine hydantoin. [(See A. Yamashiro et al., Agric. Biol. Chem., 52, 2851-2856 and 2857-2863, (1988).]

Treatment of hydantoin (I-5) with the enzyme and reaction conditions described by Yamashiro et al., should give 3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine (I-2).

The compound of formula (I-2 or I-3) produced as above is useful as an intermediate for production of the compound of formula (IV) which is useful as a non-nutritive sweetener. The sweetener compound of formula (IV) can be produced from the compound of formula (I-3) by a synthesis route summarized in the following Reaction Scheme B.

Reaction Scheme B



In the above scheme, Z represents a protective group for the amino function. (See M. Bodansky, "Principles of Peptide Synthesis," Springer-Verlag, Berlin, (1984) pp. 90-102) and R is as defined above. Typical examples of Z include the allyloxy carbonyl [I. Ninomi et al, Tet. Let., 26, 2449 (1985); O. Dangles et al., J. Org. Chem., 52, 4984-93 (1987)], the formyl (U.S. Patent Nos.: 4,684,745, 3,879,372 and 3,933,781), the t-butoxycarbonyl, [D. T. Witiak et al., J. Med. Chem. 14, 24-30 (1971)]; and the carbobenzyloxy (U.S. Patent No. 4,508,912; EP 227301; July 1, 1987). The latter is particularly useful in that it can be readily removed by catalytic hydrogenation.

In the Reaction Scheme B, the compound of formula (I-3,L-form) is reacted with an N-protected-L-aspartic acid anhydride in a non-protic solvent to yield the desired alpha-(N-protected-L-aspartyl)-3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine alkyl ester (III alpha). In addition, a small (10-20%) amount of the beta-(N-protected-L-aspartyl)-3-(2R-exo-7,7- dimethylnorbornyl)-L-alanine alkyl ester (III beta) is also produced. The amount of by-product (III beta) formed in the reaction can be controlled by variations of the reaction conditions as shown in Table 5 for Z = carbobenzyloxy (=CBZ).

Similar solvent effects on the coupling of (II) (Z=CBZ) with phenylalanine methyl ester have been observed by Yang and Su [J. Org. Chem, 51, 5186-91 (1986)] and T. Yukawa et al, EP 227301].

The undesired (III beta) can be separated from (III alpha) by partitioning between a suitable organic solvent and an aqueous buffer of the proper pH. In

previous reports of this type of separation [W. J. LeQuesne and G. T. Young, J. Chem. Soc., 24-28 (1952) and W. D. John and G. T. Young, J. Chem. Soc. 2870 (1954)], alpha/beta-N-carbobenzyloxyaspartylglycine methyl ester, alpha/beta-N-carbobenzyloxyaspartyltyrosine methyl ester, alpha/beta-N-carbobenzyloxyaspartylglutamic acid diethyl ester, and alpha/beta-N-carbobenzyloxyaspar- tyl-valine were separated by extraction of ethyl acetate solutions with aqueous sodium carbonate (concentration and pH unspecified).

In a further example alpha and beta-NCBZ-aspartylphenylalanine methyl esters were separated by extraction of the beta- isomer from ethyl acetate using buffer of about pH 6-7. (.S. Patent No. 3,808,190). No indication of the purity of the separated isomers was given.

We have found in the case of (III alpha) and (III beta) (Z=CBZ) that the pH of the aqueous phase must be carefully controlled (See Table 6). In addition, the choice of organic phase is also important. Good separation is achieved with ether and toluene, only modest partitioning with ethyl acetate and no separation at all with hexane or butanol.

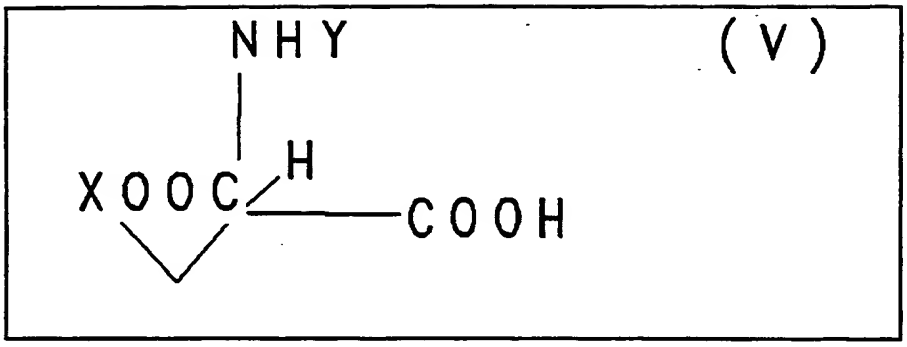
On a preparative scale, the extraction of a 1% toluene solution of the crude coupling mixture (III alpha/beta, alpha/beta=5/1, Z=CBZ) with three portions of pH 6.5, 0.1 M phosphate buffer gives (III alpha) in 50-70% yield and a purity of 93-98%. The remaining (III beta) is removed during crystallization of (IV).

Removal of the CBZ group from (III alpha) is readily achieved by hydrogenation at 2-3 kg./cm.^{2} using palladium on charcoal as catalyst in a methanol solution. The catalyst is removed by filtration through celite and the filtrate evaporated to give crude (IV). Sweetener (IV) is purified by crystallization from chloroform-hexane.

In addition we have also found that pure (IV) can be obtained from the original (III alpha-III beta) mixture (~9/1, III alpha/III beta) by hydrogenation as mentioned and repeated crystallization from methanol-water as shown in Table 7. The procedure is most effective when the (III alpha)/(III beta) ratio from the coupling reaction is high (III alpha/III beta >8/1).

A similar separation of alpha-N-aspartylphenylalanine methyl ester from the beta- isomer by crystallization from water or water-alcohol mixtures has been described previously in U.S. Patent No. 3,786,039.

An alternate coupling procedure which avoids the above formation of a product mixture of alpha- and beta-dipeptides involves performing the reaction using (I-3, R=CH_3) and a diprotected aspartic acid derivative (V)



where X = benzyl or t-butyl and Y = carbobenzyloxy or t-butoxycarbonyl. (t-BOC) [M. Bodansky, "Principles of Peptide Synthesis," Springer-Verlag, Berlin, 70-79 and 90-102 (1984)] The coupling reaction may be carried out by first converting the free carboxyl of the aspartic acid moiety to an activated leaving group by treatment with i.e. p-nitrophenol/DCC, N-hydroxysuccinimide/DCC, isobutylchoroformate/N-methylmorpholine, or the like, followed by the addition of (I-3, R=CH_3). Alternatively, it may be performed using DCC in organic solvents at a temperature range of from about -20 to 30°C. [See M. Bodansky, loc. cit., pg. 9-58; U.S. Patent No. 4,788,069 and J. W. Tsang et al., J. Med Chem, 27, 1663-1668 (1984).] The resulting intermediates may then be converted to (IV) by deprotection employing catalytic hydrogenation under standard hydrogenation conditions (Pd/C, MeOH, H_2 pressure 10-50 psig) for Y = CBZ and X = benzyl. In the case where Y = t-BOC and X = t-butyl, the deprotection may be carried out in organic solvents

employing strong acids [HCl, trifluoracetic acid (TFA) or the like] with (IV) being obtained following neutralization of the resultant salt.

The following examples illustrate the present invention more specifically.

EXAMPLE 1

Conversion of trans-2-pinanol to alpha-fenchyl alcohol.

Preparation of Catalysts

Catalysts A, B and C used in the following Runs were prepared as follows:

Catalyst A

Commercial reagent, aluminum nitrate nonahydrate [$Al(NO)_3 \cdot 9H_2O$] (a product of Junsei Chemical Co., Ltd.), 150 g., was dissolved in 800 ml. of water, and 27 ml. of 85% phosphoric acid (a product of Nacalai Tesque, Inc.) was added to the solution, and while the mixture was being stirred at room temperature 240 ml. of 10 % aqueous ammonia was slowly added dropwise to adjust its pH to 7. The resulting precipitate was left to stand overnight, filtered, thoroughly washed with water, and dried at 60°C for 24 hours to give 65 g. of product. It was powdered in a mortar to give a powder having a size smaller than 40 mesh.

Catalyst B

Hydrous niobium hydroxide ($Nb_2O_5 \cdot xH_2O$, a product of Companhia Brasileira de Metalurgia E Mineração) was pulverized to a size smaller than 40 mesh.

Catalyst C

Nickel sulfate hexahydrate ($NiSO_4 \cdot 6H_2O$, a product of Nacalai Tesque, Inc.) was calcined at 250°C or 350°C for 3 hours to reduce its size to smaller than 40 mesh.

RUN 1

Catalyst A was calcined at 300°C for 3 hours, and used in this example.

A four-necked flask equipped with a stirrer, a thermometer and a reflux condenser was charged with 35 g. (0.227 mole) of trans-2-pinanol (a product of Glidco Organics) and 2.0 g. of the catalyst, and with stirring, it was reacted at 75°C for 16 hours. The reaction product was coarsely distilled to give 29.1 g. of an oily product. Gas chromatographic analysis showed that the conversion was 98.2 %, and the selectivity of alpha-fenchyl alcohol was 48.1 %. The reaction product was rectified to give 15.3 g. (theoretical yield 42.9 %; purity 98.3 %) of alpha-fenchyl alcohol.

RUN 2

A four-necked flask equipped with a stirrer, a thermometer and a reflux condenser was charged with 35 g. (0.227 mole) of trans-2-pinanol (a product of Glidco Organics) and 2.0 g. of catalyst B, and it was reacted at 75°C for 63 hours. The reaction mixture was treated as in Example 1 and analyzed by gas chromatography. The conversion was 99.3 %, and the selectivity of alpha-fenchyl alcohol was 52.3 %.

RUN 3

Catalyst C was calcined at 250°C for 3 hours, and used in this example.

A four-necked flask equipped with a stirrer, a thermometer and a reflux condenser was charged with 35 g.

(0.227 mole) of trans-2-pinanol (a product of Glidco Organics) and 2.0 g. of the catalyst, and it was reacted at 75°C for 20 hours. The conversion was 51.0 %, and the selectivity of alpha-fenchyl alcohol was 40.6 %.

RUNS 4-16

As in Runs 1 to 3, alpha-fenchyl alcohol was produced from trans-2-pinanol using catalyst A, B or C prepared as above at the calcination temperatures and reaction temperatures indicated in Table 1. The results are shown in Table 1. In the examples, gas chromatographic analysis was carried out using a Shimadzu GC-9A (made by Shimadzu Seisakusho Ltd.) with a PEG-HT capillary 0.25mm. in diameter X 25m. in length (made by Gasukuro Kagyo Co., Ltd.). The column temperature was 100°C.

Table 1

Run	Catalyst	Calcination temperature (°C)	Reaction conditions		Conversion (%)	Selectivity of α-fenchyl alcohol (%)
			Temperature (°C)	Time (hr)		
1	A	300	75	16	98.2	48.1
2	B	-	75	63	99.3	52.3
3	C	250	75	20	51.0	40.6
4	A	300	110	6	100	41.2
5	"	500	110	6	100	36.0
6	"	800	110	3	100	35.0
7	B	-	110	18	99.3	45.4
8	"	200	75	18	97.8	46.1
9	"	200	110	4	100	34.2
10	"	300	75	22	99.4	43.2
11	"	400	75	22	99.4	42.7
12	"	500	75	19	98.5	41.7
13	"	600	75	20	34.1	40.0
14	C	250	110	18	100	24.8
15	"	350	75	18	23.9	34.4
16	"	350	110	15	97.3	20.3

Example 2. Purification of (+)-alpha-fenchyl alcohol

Commercial alpha-fenchyl alcohol ($[\alpha]_D^{23}$=+10.0°(c=5, ethanol), mp. 43.2°C; 709.2 g) was dissolved in 355 g. of n-heptane, and the solution was cooled to about -33°C. The crystals that precipitated were separated by filtration to give 493.6 g. of a first crop of crystals ($[\alpha]_D^{24}$=+11.6°, mp. 45.2°)

The residue (228.9 g.) left after evaporation of the filtrate was dissolved in 160 g. of n-heptane and the solution was cooled to -50°C. The precipitate was filtered giving 128.6 g. of a second crop of crystals ($[\alpha]_D^{24}$=+10.2°, mp. 43.2°C). These crystals were of the same quality as the starting material. They were again dissolved in 64 g. of n-heptane, and the solution was cooled to about -33°C. The crystals that precipitated were separated by filtration to obtain 94.0 g. of the crystals ($[\alpha]_D^{23}$=+11.5°, mp. 45.1°C). These crystals were combined with the first crystals (total 587.6 g.) and dissolved in 411 g. of n-heptane. The solution was cooled to about -35°C. The crystals that precipitated were separated by filtration to obtain 416.1 g. of second crystals ($[\alpha]_D^{24}$=+11.9°, mp. 45.7°C). The second crop of crystals (416.2 g.) was dissolved in 310 g. of n-heptane, and the solution was cooled to -31°C. The crystals that precipitated were separated by filtration to obtain 278.9 g. of third crystals

($[\alpha]_D^{24}$=+12.2°, mp. 46.4°C)

D

The mother liquors of the second crystals and third crystals were combined, and the solvent was recovered to yield 298.7 g. of crystals ($[\alpha]_D^{23}$=+9.84°). The resulting crystals were subjected to three cycles of crystallization in the same way as above to give 84.2 g. of fourth crystals ($[\alpha]_D^{23}$=+12.2°, mp. 46.1°C). The third crystals and fourth crystals were combined to obtain 363.2 g. of the desired (+)-alpha-fenchyl alcohol in a yield of 51.2 %.

The optical purities of the resulting crystals were measured by the method described below. The results are tabulated below.

Table 2

	Specific rotation	Optical purity (% e.e.)
Starting material	+10.0°	81
First crystals	+11.6°	89.9
Second crystals	+11.6°	92.1
Third crystals	+12.2°	94.8
Fourth crystals	+12.1°	94.6

Measurement of the Optical Purity

N-carbobenzyloxy-L-alanine (0.31 g.; 1.4 mM), 0.01 g. (0.1 mM) of N,N-dimethylaminopyridine (DMAP) and 0.2 g. (1.28 mM) of fenchyl alcohol were dissolved in 2 ml. of methylene chloride. In a stream of nitrogen under cooling, 0.27 g. (1.4 mM) of 1-ethyl-3-(3-di- methylaminopropyl)carbodiimide hydrochloride (WSC) was added to the solution, and reacted for about 30 minutes. The temperature was returned to room

temperature, and the reaction was carried out for about 1 hour. Methylene chloride was added to the reaction solution to adjust the total amount of the reaction mixture to 10 ml. It was washed with a 10% aqueous solution of citric acid, a 4% aqueous solution of sodium carbonate and a saturated aqueous solution of sodium chloride, and dried over anhydrous magnesium sulfate. The solvent was evaporated at less than 40°C. The residue was dissolved in 5 ml. of methanol and reduced with hydrogen under atmospheric pressure in the presence of 20 mg. of palladium black. The solution was analyzed by gas chromatography under the following conditions.

Column: PEG-HT, 0.25 mm. in diameter and
25 m. in length

Introduction temperature: about 200°C.

Column temperature: a range from about 100 -200°C, 3°C/min.

Retention time: a range of about 11-12 min.

Separation coefficient: 1.02

EXAMPLE 3

Preparation of alpha-fenchene from fenchyl alcohol

1. Preparation of aluminum oxide catalysts

(a) Catalyst A

Two hundred grams of aluminum nitrate nonahydrate [$Al(NO_3)_3 \cdot 9H_2O$; reagent first class produced by Junsei Chemical Co., Ltd.] was dissolved in 2 liters of water. The solution was slowly added dropwise with stirring to 500 g. of 28% aqueous ammonia. After standing, the resulting aluminum hydroxide was aged overnight, filtered, washed with water, and dried at 60°C for 24 hours to give 43 g. of aluminum hydroxide. It was powdered in a mortar and calcined in an

electric furnace at 500°C for 3 hours to give 28.4 g. of aluminum oxide as a white powder. The Hammett acidity function H_o of this product was $-5.6<H \leq -3.0$.

(b) Catalyst B

Two hundred grams of aluminum sulfate 14- to 18-hydrate [$Al_2(SO_4)_3 \cdot 14\text{-}18\ H_2O$; reagent first class produced by Junsei Chemical Co., Ltd.] was dissolved in 2 liters of water. Aqueous ammonia (10% by weight) was added dropwise to the solution until the solution reached pH 8. The resulting aluminum hydroxide was fully washed with a large amount of water, and dried at about 60°C for 24 hours. The dried product was powdered in a mortar and then calcined in an electric furnace at 500°C for 3 hours to give 70 g. of aluminum oxide as a white powder. The Hammett acidity function H_o of the product was $-5.6<H_o \leq -3.0$.

(c) Catalyst C

Two hundred grams of aluminum chloride hexa- hydrate [$AlCl_3.6H_2O$; reagent first class produced by Junsei Chemical Co., Ltd.] was dissolved in 2 liters of water, and then treated as in the preparation of catalyst B to give 62 g. of aluminum oxide. The Hammett acidity function of this product was $-5.6<H \leq -3.0$.

(d) Catalyst D

Two hundred grams of sodium aluminate [$NaAlO_2 \cdot xH_2O$; reagent first class produced by Nakarai Tesque Co., Ltd.] was dissolved in 2 liters of water. With stirring, the solution was added to an aqueous solution of hydrochloric acid (250 g/3 liters) to adjust the solution to about pH 8. The precipitate was separated by filtration, dried

at 60°C for 12 hours, and washed five times with 500 ml. of 14% aqueous ammonia. The washed product was dried at 60°C for 24 hours, powdered in a mortar, and calcined in an electric furnace at 500°C for 3 hours to give 115 g. of aluminum oxide as a white powder. The Hammett acidity function of this
product was $-5.6<H_o\leq-3.0$.

2. Production of (+)-alpha-fenchene

(a) A three-necked flask equipped with a Dean-Stark device, a stirrer, a thermometer and a reflux condenser was charged with 100 g. (0.65 mole, purity 98.7%) of alpha-fenchyl alcohol and 5 g. (5% by weight) of catalyst A, and with stirring, the mixture was heated at a temperature range from about 195 to 200°C for 10 hours. The reaction mixture was then coarsely distilled to give 95.8 g. of an oily product. Gas chromatographic analysis showed the oily product to consist of 72% of fenchene isomers (in which alpha-fenchene accounted for 59%) and 28% of unreacted fenchyl alcohol. Rectification of the oily product gave 34.4 g. of (+)-alpha-fenchene (yield 54.1%; purity 98.7%; Run No.1).

Boiling point: 157-158°C (730 mm Hg)

$([\alpha]_D^{24}=+36.27°$ (neat)

^{1}H-NMR ($CDCl_3$) :

0.97 and 0.98 (each 3H, s),
1.20 - 1.34 (2H, m),
1.65 (1H, t),
1.79 - 1.96 (3H, m)
2.03 (1H, d), 2.41 (1H, d)

4.60 and 4.81 (each 1H, s)

Mass Spectrum (m/e):

136 (M+), 121, 107, 93, 79, 53, 41, 39.

(b) Catalyst A (5%) was added to a mixture of (+)-alpha- and (+)-beta-fenchyl alcohol (alpha-/ beta-=6/4). The mixture was treated as in section (a) above to obtain an oily product. Gas chromatographic analysis showed the product to comprise 95% of fenchene isomers (in which (+)-alpha-fenchene accounted for 65%) (Run No.2).

(c) Catalyst A (5% by weight) was added to (+)-beta-fenchyl alcohol (purity 95%). The mixture was heated at a temperature range of from about 195 to 200°C for 3 hours with stirring and then coarsely distilled. Gas chromatographic analysis of the distillate showed it to comprise 98% of fenchene isomers (in which (+)-alpha-fenchene accounted for 80%) (Run No.3).

(d) Using catalysts B, C or D, (+)-alpha-fenchene was produced from (+)-alpha-fenchyl alcohol. The results are shown in Table 3 below (Runs Nos. 4 to 6).

(e) The procedure as in (a) above was repeated except that catalyst A was replaced by commercial aluminum oxide catalysts having a Hammett acidity function of $+1.5<H_o\leq+3.3$ and $+3.3<H_o\leq+4.8$.

(Runs Nos. 7 and 8), a catalyst obtained by calcining nickel sulfate hexahydrate at about 250°C for 3 hours (Run No. 9), a catalyst obtained by calcining nickel sulfate hexahydrate at about 400°C for about 3 hours (Run No. 10), aluminum sulfate (Run No. 11), a catalyst obtained by calcining aluminum phosphate at about 500°C for about 3 hours (Run No.12), aluminum silicate (Run No. 13), alum

(Run No.14) or acid clay (Run No. 15). The results are also shown in Table 3.

Table 3

Run No.	Catalyst	Starting fenchyl alcohol	Amount of the catalyst based on the fenchyl alcohol (wt%)	Reaction conditions		Total fenchene selectivity (%)	Alpha-fenchene selectivity (%)
				Temp. (°C)	Time (hr)		
1	Catalyst A	α-	5	195-200	10	72	59
2	Catalyst A	α/β=6/4	5	195-200	10	95	65
3	Catalyst A	β-	5	195-200	3	98	80
4	Catalyst B	α-	5	195-200	10	82	44
5	Catalyst C	α-	5	195-200	10	70	47
6	Catalyst D	α-	5	195-200	10	70	53
7	Active alumina	α-	10	195-200	16	20	36
8	Active alumina	α-	10	195-200	16	4	32
9	$NiSO_4 \cdot 6H_2O$	α-	50	195-200	4	100	2
10	$NiSO_4 \cdot 6H_2O$	α-	50	195-200	4	98	10
11	$Al_2(SO_4)_3$	α	50	195-200	4	88	6
12	$AlIO_4$	α-	50	195-200	16	8	23

13	Aluminum silicate	α-	50	195-200	6	97.5	0
14	Alum	α-	50	195-200	16	77.4	1
15	Acid clay	α-	5	195-200	7	94.8	4

The fenchenes were analyzed by gas chromatography using a gas chromatographic device ("Shimazu" GC-9A made by Shimazu Seisakusho Co., Ltd.) using an OV-1 silica capillary column (diameter 0.25 mm., length 25 m.); made by Gasukuro Kogyo Co., Ltd.) at a temperature of about 70°C.

EXAMPLE 4

Production of 7,7-dimethyl-2-formylmethylenenorbornane:

Fifty grams (0.368 mole) of (+)-alpha-fenchene obtained as in Example 3 was added dropwise under a nitrogen stream at 50 to 60°C over about 1 hour to a solution which had been prepared by adding 38 ml. (0.415 mole) of $POCl_3$ to 92.5 ml. (1.19 mole) of DMF over about 1 hour. The mixture was reacted for 2 hours. The reaction solution was poured into 800 ml. of a 10% aqueous solution of sodium carbonate, and extracted twice with 300 ml. of toluene. The combined toluene extracts were washed with water, and the solvent was evaporated. Fractional distillation under reduced pressure gave 50.5 g. (yield 71%) of the captioned compound.

Boiling point: 76 - 80°C/1 mm Hg

^{1}H-NMR ($CDCl_3$ solvent, TMS internal standard, δ):

E-form

0.98 and 1.08 (each 3H, s, CH_3), 5.94 (1H, d, J=7.9 Hz, olefinic H) and 9.79 (1H, d, J=7.9 Hz, CHO).

Z-form

0.97 and 1.08 (each 3H, s, CH_3), 5.86 (1H, d, J=8.4 Hz, olefinic H), 9.84 (1H, d, J=8.3 Hz, CHO).

Mass Spectrum (m/e):

E-form

150, 125, 109, 107, 82, 81 (base), 79, 67 and 41.

Z-form

165 (M^++1), 164 (M^+), 149, 121 (base), 93, 91, 79, 77, 41 and 39.

EXAMPLE 5

Production of 2R-exo-7,7-dimethylnorbornyl acetaldehyde:

(a) A 1 liter autoclave was charged with 20 g. (0.12 mole) of 7,7-dimethyl-2-formylmethylenenorbornane obtained as in Example 4 above, 200 ml. of n-heptane and 0.5 g. of 5% palladium-carbon, and the reaction was carried out at room temperature under a hydrogen pressure of 2 kg./cm.^{2}. After the reaction, the catalyst was filtered and the solvent was evaporated. The residue was distilled under reduced pressure to give 19.7 g. (yield 97.3%) of the captioned compound. The exo/endo ratio of this compound was found to be 98:2 by measurement of ^{1}H-NMR.

Boiling point: 54 - 55°C/0.2 mm Hg

^{1}H-NMR ($CDCl_3$ solvent, TMS internal standard, δ):

Exo-form

0.97 and 1.08 (each 3H, s, CH_3), 2.60 (2H, d, d, d, J=2.1, 9.6, 5.9 Hz; $C\underline{H}_2CHO$)) and 9.71 (1H, t, J=7.9Hz; $C\underline{H}O$).

Endo-form

1.02 and 1.08 (each 3H, s, CH_3), 9.76 (1H, t, J=7.9 Hz, $C\underline{H}O$).

Mass Spectrum (m/e): 166 (M^+), 151, 133, 123, 122 (base), 107, 95, 81, 79, 69, 67, 55, 41.

(b) A 200 ml. autoclave was charged with 5.0 g. (0.037 mole) of (+)-alpha-fenchene obtained as in Example 3, 45.3 mg. (0.18 mmole) of the dimer of rhodium (I) chloride-1,5-cyclooctadiene, 95 mg. (0.36 mmole) of triphenylphospine, 0.5 ml. of triethylamine and 25 ml. of benzene, and the reaction was carried out at 90°C for 16 hours under a synthesis gas pressure of 80 kg./cm.^{2} (carbon monoxide pressure 40 kg./cm.^{2}; hydrogen pressure 40 kg./cm.^{2}). The solvent was evaporated, and the residue was fractionally distilled under reduced pressure to give 5.7 g. (yield 93.4%) of an exo/endo mixture of 7,7-dimethylnorbornyl-2-acetaldehyde. The (2R)-exo/(2S)-endo ratio of the product was determined to be 85:15 by ^{1}H-NMR.

(c) 7,7-Dimethylnorbornyl-2-acetaldehyde having the (2R)-exo/(2S)-endo ratios shown in Table 4 was obtained by carrying out the oxo reaction as in (b) above under the conditions shown in Table 4.

Table 4

Run No.	Oxo reaction catalyst	Reaction conditions		Yield (%)	Exo/endo ratio
		temp. (°C)	time (hr)		
2	$[CODRhCl)_2 \cdot 2pph3$*	50	64	35	89/11
3	$Rh_6(CO)_{16}$	70	18	80	66/34
4	$Rh_6(CO)_{16} \cdot 2pph3$	70	17	81	87/13

*COD = 1,5-Cyclooctadiene

EXAMPLE 6

Production of 3-(2R-exo-7,7-dimethylnorbornyl) 2-D,L-amino propionitrile:

Ammonia gas was passed through 400 ml. of methanol at 5°C for 15 minutes. To the resulting solution were added 17.5 g. (0.357 mole) of sodium cyanide, 17.8 g. (0.333 mole) of ammonium chloride and 52.0 g. (0.313 mole) of (2R-exo-7,7-dimethylnorbornyl) acetaldehyde. The reaction mixture was stirred overnight at room temperature and the methanol was evaporated under reduced pressure. To the residue was added 750 ml. of a 2% aqueous solution of sodium carbonate, and the mixture was extracted with 350 ml. of ether twice. The extracted ether layers were washed with water, and then extracted with 300 ml. of 1 N hydrochloric acid twice. The extracted hydrochloric acid layers were neutralized with sodium carbonate and further extracted with 300 ml. of ether three times. The extracts were dried over anhydrous sodium sulfate and the solvent was evaporated to give 3-(2R-exo-7,7-dimethylnorbornyl)-2-D,L-amino propionitrile as a pale yellow oil in a yield of 95.5%.

^{1}H-NMR (CD_3OD solvent, TMS internal standard, δ): 1.07 and 1.11 (each 3H, s, CH_3) and 4.38 - 4.49

(1H, m, $\underline{CH}<^{CN}_{N}$) (as amino propionitrile hydrochloride)

EXAMPLE 7

Production of 3-(2R-exo-7,7-dimethylnorbornyl)-D,L-alanine hydrochloride:

52.0 g. (0.271 mole) of 3-(2R-exo-7,7-dimethylnorbornyl)-2-D,L-amino propionitrile was added to 200 ml. of water and 900 ml. of concentrated hydrochloric acid, and the mixture was heated under reflux for 18 hours. The reaction solution was concentrated under reduced pressure and then cooled. Amino acid hydrochloride precipitated. It was left to stand overnight at 5°C, filtered, and washed with 600 ml. of ether to give 63.2 g. of 3-(2R-exo-7,7-dimethylnorbornyl)-D,L-alanine hydrochloride in a yield of 94.1%.

^{1}H-NMR (CD_3OD solvent, TMS internal standard, δ): 1.02 and 1.11 (each 3H, s, CH_3) and 4.37-4.42 (1H, m, $\underline{CH}<^{CO_2H}_{N}$)

The amino acid was prepared by neutralization of the hydrochloride and precipitation at pH 4.0. Melting point: 216-218°C, IR: 3400, 2930, 1610, 1495, 1395, 1330 and 1100 cm-1.

EXAMPLE 8

Optical resolution of 3-(2R-exo-7,7- dimethylnorbornyl)-D,L-alanine methyl ester by the tartaric acid method:

To a solution of 36.5 g. of 3-(2R-exo-7,7 dimethyl-norbornyl)-D,L-alanine methyl ester (prepared from 3-(2R-exo-7,7-dimethylnorbornyl)-D,L-alanine as described in Example 15) in 500 ml. of methanol was added a solution of 25.7 g. of D-(-)-tartaric acid in 500 ml. of methanol. The solution was diluted to 1800 ml. with methanol, then heated to reflux to dissolve the precipitate which had formed. Crystallization was obtained by allowing the hot solution to stand at about 21°C overnight. Filtration, washing with 50 ml. of methanol and drying in vacuo gave 24.1 g.

The above material was recrystallized from 850 ml. of methanol to give 13.1 g. This in turn was recrystallized from 450 ml. of methanol to afford 8.8 g. of 3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine methyl ester-D-tartrate salt.
Melting point: 160°C (decompose)
$[\alpha]_D^{20}$ = + 36.4 (c = 0.5, MeOH)

EXAMPLE 9

Synthesis of N-acetyl-3-(2R-exo-7,7-dimethylnorbornyl)-D,L-alanine:

3-(2R-exo-7,7-dimethylnorbornyl)-D,L-alanine hydrochloride (60 g.; 0.242 mole) was dissolved in 300 ml. of a 10% aqueous solution of NaOH, and then 32 g. (0.314 mole) of acetic anhydride was added dropwise at 35 to 40°C. After the addition, they were reacted for 30 minutes. The reaction solution was cooled to 5 to 10°C, and adjusted to pH 3 with 6 N hydrochloric acid. The precipitated crude crystals were filtered, washed with water and dried. The crude crystals were recrystallized from ethyl acetate and n-hexane to give 60 g. (yield 97.6%) of the captioned compound.

Melting point: 170 - 171°C

$[\alpha]_D^{24}$ =+36.6° (c=1, methanol)

1H-NMR (CD_3^{OD} solvent, TMS internal standard, δ):

0.98 and 1.09 (each 3H, s, CH3), 1.98 (3H, s, NHCOCH3) and 4.31 - 4.39 (1H, m, CH<, CO2 / NHAc)

EXAMPLE 10

Optical resolution of N-acetyl-3-(2R-exo-7,7-dimethylnorbornyl)-D,L-alanine:

A 4 N aqueous solution of NaOH was added to a slurry composed of 450 ml. of water, 28.8 g. of disodium hydrogen phosphate, 30 mg. of cobalt chloride hexahydrate and 60 g. (0.236 mole) of N-acetyl-3-(2R- exo-7,7-dimethylnorbornyl)-D,L-alanine to adjust the pH to 8.0. A solution of 1.12 g. of acylase (a product of Amano Pharmaceutical Co., Ltd.) in 12 ml. of phosphate buffer (pH 8.0), was added and the mixture stirred at 37 to 39°C for 20 hours. The reaction solution was adjusted to pH 1.4 with concentrated hydrochloric acid, and washed with 200 ml. of ethyl acetate three times. The aqueous layer was adjusted to pH 3.0 with aqueous ammonia. The crude crystals that precipitated were separated by filtration. The resulting crude crystals (18.3 g.) were dissolved in 800 ml. of hot water, and treated with 1.8 g. of activated carbon to give 17.7 g. (yield 71.1%) of 3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine.

Melting point: 224 - 226°C

$[\alpha]^{23}_{D}$ =+49.5° (c=1, methanol)

1H-NMR (CD3OD solvent, TMS internal standard, δ):

0.99 and 1.11 (each 3H, s, CH3) and

3.44-3.47 (1H, m, CH-CO2)
　　　　　　　　　　|
　　　　　　　　　　NH2

Separately, the ethyl acetate washings were concentrated to give crude crystals (34.9 g.). The crude crystals were recrystallized from ethyl acetate and n-hexane to give 26.6 g. (yield 88.7%) of N-acetyl-3-(2R-exo-7,7-dimethylnorbornyl)-D-alanine having a specific rotation of +4.1° (c=1, methanol).

EXAMPLE 11

Racemization of N-acetyl-3-(2R-exo-7,7-dimethyl-norbornyl)-D-alanine:

Ten grams (0.039 mole) of N-acetyl-3-(2R-exo-7,7-dimethylnorbornyl)-D-alanine obtained in Example 10 was dissolved in 50 ml. of acetic acid and 1.0 g. of acetic anhydride, and reacted at 100°C for 16 hours. After cooling, the reaction mixture was concentrated under reduced pressure. The resulting crude crystals were dissolved in 35 ml. of ethyl acetate and washed with water. The ethyl acetate layer was crystallized by adding n-hexane to give 6.8 g. of N-acetyl-3-(2R-exo-7, 7-dimethylnorbornyl)-D,L-alanine having a specific rotation of +35.5° (c=1, methanol).

EXAMPLE 12

Synthesis of N-chloroacetyl-3-(2R-exo-7,7-dimethylnorbornyl)-D,L-alanine:

Ten grams (47.4 mmoles) of 3-(2R-exo-7,7-dimethyl-norbornyl)-D,L-alanine was suspended in 120 ml. of ethyl acetate, and 35.36 g. (47.4 mmoles) of chloroacetyl chloride was added. The mixture was heated under reflux for 1 hour. After cooling, the unreacted amino acid was separated by filtration, and the ethyl acetate was evaporated. The resulting crude crystals were recrystallized from ether and n-hexane to give 10.1 g. (yield 63%) of the captioned compound.

Melting point: 149 - 150°C

$[\alpha]_D^{23}$ = +22.2° (c=1, methanol)

1H-NMR (CD_3OD solvent, TMS internal standard, δ):
0.98 and 1.09 (each 3H, s, CH_3),4.07 (2H, d,
J=10.7 Hz, $NHCOCH_2Cl$), 4.36 - 4.44 (1H, m, $\underline{C}HCO_2$)
|
NH-

EXAMPLE 13

Optical resolution of N-chloroacetyl-3-(2R-exo-7,7-dimethylnorbornyl)-D,L-alanine:

A 4 N aqueous solution of NaOH was added to a slurry composed of 300 ml. of water, 24.1 g. of disodium hydrogen phosphate, 25.5 mg. of cobalt chloride hexahydrate and 50.0 g. (0.173 mole) of N-chloroacetyl-3-(2R-exo-7,7-dimethylnorbornyl)-D,L- alanine to adjust the pH to 8.0. A solution of 0.85 g. of acylase (a product of Amano Pharmaceutical Co., Ltd.) in 42.5 ml. of 0.5 M phosphate buffer (pH 8.0), was added and the mixture stirred at 37 to 39°C for 16 hours. The reaction solution was adjusted to pH 1.7 with concentrated hydrochloric acid, and washed with 350 ml. of ethyl acetate twice. The aqueous layer was adjusted to about pH 3.0 with aqueous ammonia. The crude crystals that precipitated were separated by filtration. The resulting crude crystals (10.3 g.) were dissolved in 800 ml. of hot water, and treated with 1.4 g. of activated carbon to give 10.3 g. (yield 56.3%) of 3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine.

Separately, the ethyl acetate washings were concentrated, and the residue was recrystallized from ether and n-hexane to give 20.4 g. (yield 81.6%) of N-chloroacetyl-3-(2R-exo-7,7-dimethylnorbornyl)-D- alanine.

Melting point: 150 - 153°C

$[\alpha]_D^{23}$ = +14.1° (c=1, methanol)

EXAMPLE 14

Production of 3-(2R-exo-7,7-dimethylnorbornyl)-L- alanine methyl ester:

Hydrogen chloride gas (12.5 g.) was bubbled into 1 liter of methanol, and 52.0 g. (0.210 mole) of 3-(2R- exo-7,7-dimethylnorbornyl)-L-alanine hydrochloride was added. The mixture was heated under reflux for 18 hours. After cooling, the solvent was evaporated under reduced pressure. The residue was dissolved in 750 ml. of water, and the pH of the solution was adjusted to about 8.5 with a 50% aqueous solution of NaOH under cooling. The reaction mixture was extracted with 250 ml. of ethyl acetate twice and dried over anhydrous sodium sulfate. The solvent was evaporated to give 47.2 g. (yield 99.9%) of 3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine methyl ester as a pale yellow oil.

The product (45.0 g.; 0.2 mole) was dissolved in 80 ml. of ethyl acetate and 13.2 g. (0.22 mole) of acetic acid was added under cooling and stirring. The crystals which precipitated were collected by filtration to give 48.8 g. of the acetic acid salt of the above-captioned compound having a melting point of 101 to 104°C.

EXAMPLE 15

Production of 3-(2R-exo-7,7-dimethylnorbornyl)-D, L-alanine methyl ester:

To a solution of 12.5 g. of hydrogen chloride gas in 1 liter of methanol was added 52.0 g. of 3-(2R-exo-7,7-dimethylnorbornyl)-D,L-alanine hydrochloride. The solution was heated at reflux for 18 hours, then the product isolated

as described in Example 14 to give the title compound (44.9 g.) as a pale yellow oil.

$[\alpha]_D^{23}$ = (as the hydrochloride) = +29.5°

(C=1.2, methanol)

EXAMPLE 16

Production of L-aspartyl-3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine methyl ester:

24.9 g. (0.1 mole) of N-carbobenzyloxy-L-aspartic anhydride was suspended in 500 ml. of toluene, and the suspension was cooled to 5°C. With stirring, a suspension of 28.5 g. (0.1 mole) of 3-(2R-exo-7,7- dimethylnorbornyl)-L-alanine methyl ester acetate in 50 ml. of toluene was added. The mixture was then stirrred overnight at 5°C. The solution was subjected to a countercurrent distribution-type chromatographic device to obtain 33.5 g. (70.6 %) of N-(carbobenzyloxy -L-aspartyl)-3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine methyl ester. In a 1-liter autoclave, 25.8 g. (54.4 mmoles) of N-(carbobenzyloxy-L-aspartyl)-3-(2R-exo- 7,7-dimethylnorbornyl)-L-alanine methyl ester was dissolved in 400 ml. of methanol, and catalytically reduced in the presence of 1.0 g. of 5% palladium carbon under a hydrogen pressure of 3 kg./cm.^{2}. After the decrease of the hydrogen pressure was no longer observed, the catalyst was removed by filtration through Celite. The filtrate was concentrated under reduced pressure to give crude crystals. Recrystallization from chloroform/n-hexane gave 14.4 g. (yield 77.8%) of the desired L-aspartyl-3-(2R-exo-7,7-dimethylnorbornyl)-L- alanine methyl ester.

Melting point: 148 - 148.2°C

$[\alpha]_D^{23}$ = +30.5° (c=1, methanol)

^{1}H NMR (CD_3OD solvent, TMS internal standard, δ):
0.98 and 1.10 (each 3H, s, CH_3), 2.53
(1H, dd, J=9.7 and 16.0 Hz, CH_2CO_2H),
2.78 (1H, dd, J=4.7 and 17.1 Hz, CH_2CO_2H),
4.09 (1H, q, J=4.64 Hz, $-C\underline{H}CH_2CO_2H$), 4.41
(1H, q, J=5.4Hz, $C\underline{H}CO_2Me$)
|
NHCO

EXAMPLE 17

Production of (N-CBZ-L-aspartyl-beta-0-benzyl)-3-(2R- exo-7,7-dimethylnorbornyl)-L-alanine methyl ester:

43 g. of the 3-(2R-exo-7,7-dimethylnorbornyl)-L- alanine methyl ester-D-tartrate was suspended in an excess of a 5% Na_2CO_3 solution and stirred vigorously at 23°C for 30 minutes to give the free amino ester. This mixture was extracted with 2 x 500 ml. of EtOAc and the combined EtOAc layers dried over $MgSO_4$ (anh.). The EtOAc solution was filtered, the filtrate concentrated under reduced pressure and dried in vacuo to give 22.5 g. of
the amino ester as a clear oil. $[\alpha]_D^{23}$ + 61.8° (c=2.2, dioxane).

The above 22.5 g. of amino ester was dissolved in 800 ml. of dioxane under N_2. This was followed by the addition of 35 g. of N-CBz-L-aspartic acid-ß-benzyl ester, 24.8 g. of 1,3-dicyclohexylcarbodiimide and 12.4 g. of N-hydroxy-5-norbornene-2,3-dicarboximide. This mixture was then stirred overnight, during which time a solid precipitated.

The solid 1,3-dicyclohexylurea was removed by filtration and the filtrate concentrated under reduced pressure. The residue was taken up in 1000 ml. of ether and washed with

2 x 1000 ml. of 5% citric acid, 2 x 1000 ml. of 7% $NaHCO_3$ and 200 ml. of saturated NaCl solution. The ether solution was then dried over $MgSO_4$ (anh.), filtered and the filtrate concentrated under reduced pressure.

The residue was chromatographed on silica gel using hexane with increasing amounts of EtOAc as the eluent. The progress of the column was monitored by TLC (silica gel-40% EtOAc/Hexane) and the appropriate fractions combined to give, following concentration, 49.7 g. of the titled compound.

Melting point: 62-64°C

$[\alpha]_D^{23}$ =+9.5° (c=1, methanol)

^{1}H-NMR ($CDCl_3$ solvent, TMS internal standard, δ):

0.95 and 1.05 (each 3H, s, $-CH_3$), 3.70

(3H, s, $-OCH_3$),

5.15 (4H, s, $-CH_2$-Ar), 7.35 (10H, s, Ar)

EXAMPLE 18

Production of L-aspartyl-3-(2R-exo-7,7-dimethylnorbor- nyl)-L-alanine methyl ester:

To 8.6 g. of N-(β-benzyl-N-CBZ-L-aspartyl)-3-(2R-exo-7, 7-dimethylnorbornyl)-L-alanine methyl ester in 200 ml. of methanol was added 0.4 g. of 10% palladium/carbon. The mixture was hydrogenated at 3 kg./cm.^{2} H_2 and room temperature for 18 hours. The catalyst was then removed by filtration through a short pad of celite and the filtrate evaporated to give 5.2 g. of the title compound as a clear glass. This was crystallized from chloroform/hexane to afford material comparable to that of Example 16 as determined by HPLC, IR and ^{13}C NMR comparison.

Melting point: 144-146 °C

$[\alpha]^{23}$ = +29.2° (c=1, methanol)

D

^{1}H NMR (CD_3OD solvent, TMS internal standard, δ):

1.0 and 1.1 (each 3H, s, $-CH_3$)

2.75 (1H, m, $-CH_2-CO_2H$)

3.75 (3H, s, $-OCH_3$)

EXAMPLE 19

Purification of alpha-L-aspartyl-3-(2R-exo-7,7-dimethyl-norbornyl)-L-alanine methyl ester:

A 60.4 g. sample of α/ß-L-aspartyl-3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine methyl ester (alpha/beta =90/10) was dissolved by heating in 900 ml. of a 1:2 methanol:water mixture. Cooling the solution afforded 51.2 g. of a white solid (alpha/beta = 94.6/5.4). Repeated crystallization from the same solvent mixture (15:1 vol./wt.) as shown in Table 7 gave IV (alpha/beta = 99.2/0.8).

EXAMPLE 20

Synthesis of 3-(2R-exo-7,7-dimethylnorbornyl)alanine hydantoin:

To a solution of 2 g. (12.2 mmole) of 2R-exo-7,7-dimethylnorbornyl acetaldehyde in 35 ml. of 60% EtOH-H_2O was added 3.5 g. of $(NH_4)_2CO_3$ and the resulting slurry warmed to 55°C. To this mixture was added 650 mg. (13.2 mmole) of NaCN in 5 ml. of H_2O and the resulting mixture heated at 60°C overnight under a reflux condenser. The condenser was removed and the solution warmed to 90°C for three hours to drive off excess $(NH_4)_2CO_3$.

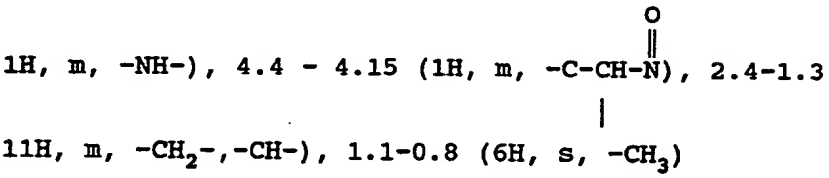
Upon cooling to room temperature, 10 ml. of H_2O was added and the solution extracted with 20 ml. of hexane. The aqueous phase was then acidified to pH 5 (to be carried out under a hood) with 1 N HCl to give a white solid precipitate. This

was removed by filtration and dried in vacuo to afford 3.1 g. of the desired product.

Melting point: 178-183°C;

IR: 3280, 2950, 1720, 1420, 1315 and 1190 $cm.^{-1}$

^{1}H-NMR (Pyridine-d_5, TMS, δ): 9.25-9.05



(1H, m, -NH-), 4.4 - 4.15 (1H, m, -C-CH-N), 2.4-1.3

(11H, m, $-CH_2-$,-CH-), 1.1-0.8 (6H, s, $-CH_3$)

EXAMPLE 21

Hydrolysis of 3-(2R-exo-7,7-dimethylnorbornyl)alanine hydantoin:

A mixture of 500 mg. of 3-(2R-exo-7,7-dimethylnorbornyl)alanine hydantoin (2.12 mmoles), 2.5 g. of barium hydroxide and 10 ml. of H_2O was heated at reflux for 72 hours. Upon cooling 20 ml. of H_2O was added and the mixture acidified to pH 2.0 with 1 N H_2SO_4. The solid was removed by filtration and the filtrate adjusted to pH 4.0 with 1 N NaOH. Concentration of the solution to ~ 10 ml. and cooling to 5°C gave a white solid. After drying in vacuo the yield was 83 mg. (0.39 mmole, 19%) of 3-(2R-exo-7,7-dimethylnobornyl)-D,L-alanine. Melting point: 217-219°C;, IR: 3430, 2950, 1610, 1505, 1400, 1320 and 1100 cm^{-1}.

Table 5

Solvent		IIIα/IIIβ	Dielectric Constant
Acetic Acid		4.5	6.15
Acetone		0.9	20.7
Acetonitrile		1.3	37.5
Ethyl Acetate		3.6	6.02
Ethyl Ether	*	7.7 (3.5)	4.34
Dioxane		2.2	2.21
Toluene	*	8.6	2.38
Butyl Acetate		4.2	5.01
Carbon Tetrachloride	*	5.0	2.24
Trichloroethylene		5.6	3.4
Tetrahydrofuran		1.4	
Chloroform		5.1	4.81
Diglyme		0.27	
Hexane	*	1.5	1.89
Dimethylformamide		0.08	37.6
Cyclopentanone		1.7	18.0
Xylene	*	7.6	2.27
Butyl Ether	*	6.8	3.0

* N-Carbobenzyloxyaspartic anhydride was insoluble (suspension) at 5°C.

Reaction of one part N-carbobenzyloxy aspartic anhydride (II) with one part 3-(2R-exo-7,7-dimethyl- norbornyl)-L-alanine methyl ester acetic acid salt in 100 parts solvent at 5°C for 18 hours. Ratios of (III alpha)/(III beta) were determined by peak heights on HPLC using an Altex 5u C_{18} column

with 60% acetonitrile/0.05M KH_2PO_4, pH 4.0 as solvent and UV detection at 210 nm.

Table 6

	III α	III β
pH 6.0	93/7	83/17
pH 6.5	87/13	17/83
pH 7.0	19/81	9/91

Partition of alpha- and beta-(N-carbobenzyloxy-L-aspartyl)-3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine methyl ester (III α/β) between toluene and 0.1 M phosphate buffers at the pH indicated. The ratios indicate the percent in the toluene phase over the percent in the buffer phase. Values are for 100 mg. of compound in 10 ml. of toluene and 10 ml. of buffer.

Table 7

Amount of material	IV α/β ratio
1. 1.482	89.9/10.1
2. 1.265	94.6/ 5.4
3. 1.129	97.1/ 2.9
4. 1.073	98.4/ 1.6
5. 1.000	99.2/ 0.8

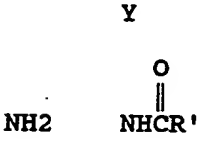
Recrystallization of a mixture of (IV alpha) and (IV beta) from 33% methanol-water. Alpha/beta ratios were determined by peak heights on HPLC using a unisil Q C18 column with 40% acetonitrile/1% methanol/ 59% 0.1 M KH_2PO_4, pH=4.0 as solvent and UV detection at 220 nm. (UNISIL Q C18: particle size 5μm, Gasukuto Kogyo Co. Ltd.)

While specific embodiments of the invention have been shown and described in detail to illustrate the application of the inventive principles, the invention may be embodied otherwise without departing from such principles.

CLAIMS

What is claimed is:

1. A compound represented by the following formula



(I)

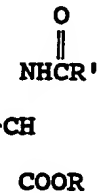
wherein Y is -CHO, -CH(CN)-, -CH(COOR)- or

wherein R is hydrogen or a lower alkyl group of one to three carbons and wherein R' is hydrogen or a lower alkyl group of one to three carbons.

2. The compound recited in claim 1, wherein Y is -CHO.

3. The compound recited in claim 1, wherein Y is

4. The compound recited in claim 1, wherein Y is



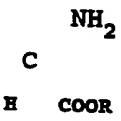
5. The compound recited in claim 4, wherein R' is -CH3 or $-CH_2Cl$.

6. The compound recited in claim 1, wherein Y is

7. A fenchyl alcohol dehydration catalyst comprising calcined aluminum hydroxide.

8. The dehydration catalyst recited in claim 7, comprising calcined aluminum hydroxide having Hammett acidity of $-5.6<H°\leq-3.0$.

9. A process for making 3-(2R-exo-7,7-dimethyl-norbornane)-L-alanine lower alkyl ester represented by the following formula:



wherein R represents a lower alkyl group of one to three carbons comprising the steps of:

(a) dehydrating-isomerizing (+)-alpha-fenchyl alcohol to form (+)-alpha-fenchene;

(b) converting the (+)-alpha-fenchene to 2R-exo-7,7-dimethylnorbornyl acetaldehyde;

(c) converting 2R-exo-7,7-dimethylnorbornyl acetaldehyde to 3-(2R-exo-7,7-dimethylnorbornyl)-D,L- alanine;

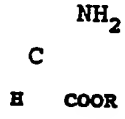
(d) resolving 3-(2R-exo-7,7-dimethylnor- bornyl)-D,L-alanine to produce 3-(2R-exo-7,7-dimethyl- norbornyl)-L-alanine; and

(e) esterifying 3-(2R-exo-7,7-dimethylnorbor- nyl)-L-alanine to form 3-(2R-exo-7,7-dimethylnorbornyl)- L-alanine lower alkyl ester.

10. The process recited in claim 9, wherein step (c) comprises converting the acetaldehyde to an amino nitrile and hydrolyzing the nitrile to form 3-(2R-exo-7,7-dimethylnorbornyl)-D,L-alanine.

11. The process recited in claim 9, wherein step (c) comprises converting the acetaldehyde to a hydantoin and hydrolyzing the hydantoin to form 3-(2R-exo-7,7-dimethylnorbornyl)-D,L-alanine.

12. A process for making 3-(2R-exo-7,7-dimethyl-norbornane)-L-alanine lower alkyl ester represented by the following formula:



wherein R represents a lower alkyl group of one to three carbons comprising the steps of:

(a) dehydrating-isomerizing (+)-alpha-fenchyl alcohol to form (+)-alpha-fenchene;

(b) converting the (+)-alpha-fenchene to 2R-exo-7,7-dimethylnorbornyl acetaldehyde;

(c) converting 2R-exo-7,7-dimethylnorbornyl acetaldehyde to 3-(2R-exo-7,7-dimethylnorbornyl)-D,L- alanine;

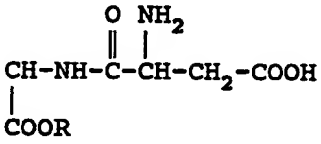
(d) esterifying 3-(2R-exo-7,7-dimethylnorbor- nyl)-D,L-alanine to form 3-(2R-exo-7,7-dimethylnorbor- nyl)-D,L-alanine lower alkyl ester; and

(e) resolving 3-(2R-exo-7,7-dimethylnor- bornyl)-D,L-alanine lower alkyl ester to produce 3-(2R-exo-7,7-dimethyl- norbornyl)-L-alanine lower alkyl ester.

13. The process recited in claim 12, wherein step (c) comprises converting the acetaldehyde to an amino nitrile and hydrolyzing the nitrile to form 3-(2R-exo-7,7-dimethylnorbornyl)-D,L-alanine.

14. The process recited in claim 12, wherein step (c) comprises converting the acetaldehyde to a hydantoin and hydrolyzing the hydantoin to form 3-(2R-exo-7,7-dimethylnorbornyl)-D,L-alanine.

15. A process for producing alpha-L-aspartyl-(2R- exo-7,7-dimethylnorbornyl)-L-alanine lower alkyl ester represented by the following formula:



wherein R represents a lower alkyl group of one to three carbons comprising the steps of:

(a) coupling 3-(2R-exo-7,7-dimethylnorbor- nyl)-L-alanine lower alkyl ester with an N-protected aspartic acid anhydride to produce an N-protected (alpha, beta)-L-aspartyl-3-(2R-exo-7,7-dimethylnorbornyl)-L- alanine lower alkyl ester;

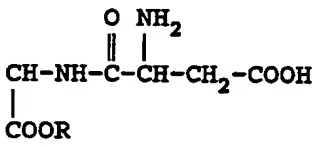
(b) deprotecting the N-protected (alpha, beta)-L-aspartyl-3-(2R-exo-7,7-dimethylnorbornyl)-L- alanine lower alkyl ester to produce a mixture of (alpha, beta)-L-aspartyl-

3-(2R-exo-7,7-dimethylnorbor- nyl)-L-alanine lower alkyl ester; and

(c) separating the alpha-L-aspartyl-3- (2R-exo-7,7-dimethylnorbornyl)-L-alanine lower alkyl ester from the mixture.

16. The process recited in claim 15 wherein an N-protected aspartic acid having a beta-ester protecting group is utilized for the N-protected aspartic acid anhydride.

17. A process for producing alpha-L-aspartyl-(2R- exo-7,7-dimethylnorbornyl)-L-alanine lower alkyl ester represented by the following formula:



wherein R represents a lower alkyl group of one to three carbons comprising the steps of:

(a) coupling 3-(2R-exo-7,7-dimethylnorbor- nyl)-L-alanine lower alkyl ester with an N-protected aspartic acid anhydride to produce an N-protected (alpha, beta)-L-aspartyl-3-(2R-exo-7,7-dimethylnorbornyl)-L- alanine lower alkyl ester;

(b) separating the N-protected alpha-L-aspartyl-3- (2R-exo-7,7-dimethylnorbornyl)-L-alanine lower alkyl ester from the mixture; and

(c) deprotecting the N-protected alpha-L-aspartyl-3- (2R-exo-7,7-dimethylnorbornyl)-L-alanine lower alkyl ester to produce alpha-L-aspartyl-3-(2R-exo-7,7- dimethylnorbornyl)-L-alanine lower alkyl ester.

18. A process for purifying (+)-alpha-fenchyl

alcohol, which comprises crystallizing alpha-fenchyl alcohol in a hydrocarbon solvent at low temperatures.

19. A process according to claim 18 in which the solvent is n-heptane or n-octane and the temperature range -35 to -60°C.

20. A process for producing alpha-fenchene, which comprises heating fenchyl alcohol in the presence of an aluminum oxide catalyst.

21. A process according to claim 20 where the catalyst is calcined aluminum oxide having a Hammett acidity function $-5.6<H_o\leq-3.0$.

22. A process for producing an optically active 3-(2R-exo-7,7-dimethylnorbornyl)-L-alanine or its lower alkyl ester, which comprises treating an N-acyl-3-(2R-exo-7,7-dimethylnorbornyl)-D,L-alanine or its lower alkyl ester with an acylase in an aqueous medium, and recovering the resulting 3-(2R-exo-7, 7-dimethylnorbornyl)-L-alanine or its lower alkyl ester.

23. The process recited in claim 22, wherein the N-acyl is selected from the group consisting of N-acetyl and N-chloroacetyl.

24. The process recited in claim 22, wherein the acylase is Amano acylase I.

25. A process for producing alpha-fenchyl alcohol, which comprises reacting trans-2-pinanol in the presence of at least one catalyst selected from the group consisting of aluminum phosphate, niobium oxide and nickel sulfate at a temperature of 60 to 150°C.